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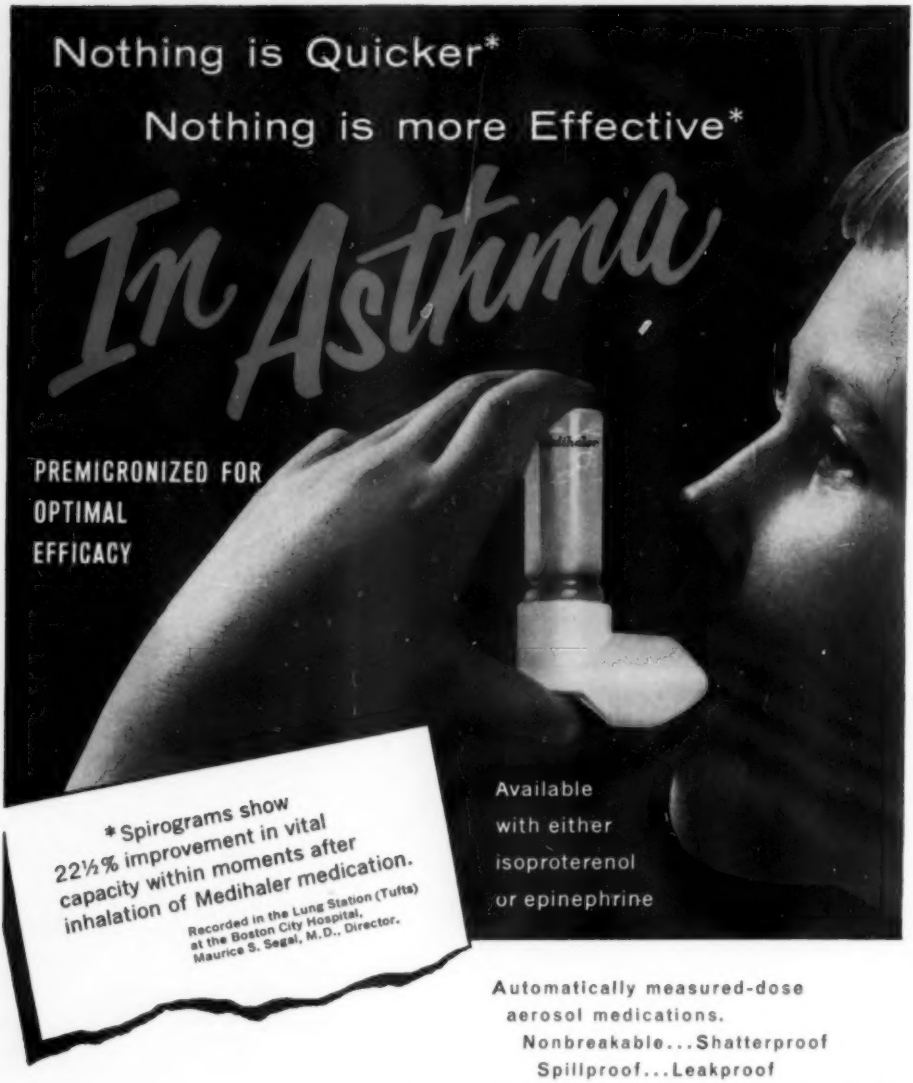
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Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street. Chicago 10.

AMERICAN MEDICAL ASSOCIATION Publication

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee.

Second-class postage paid in Nashville, Tennessee.

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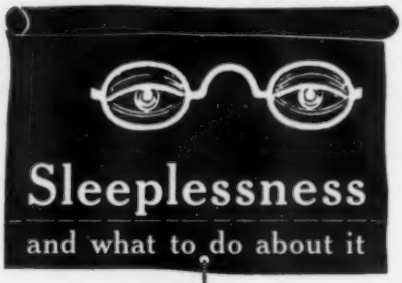

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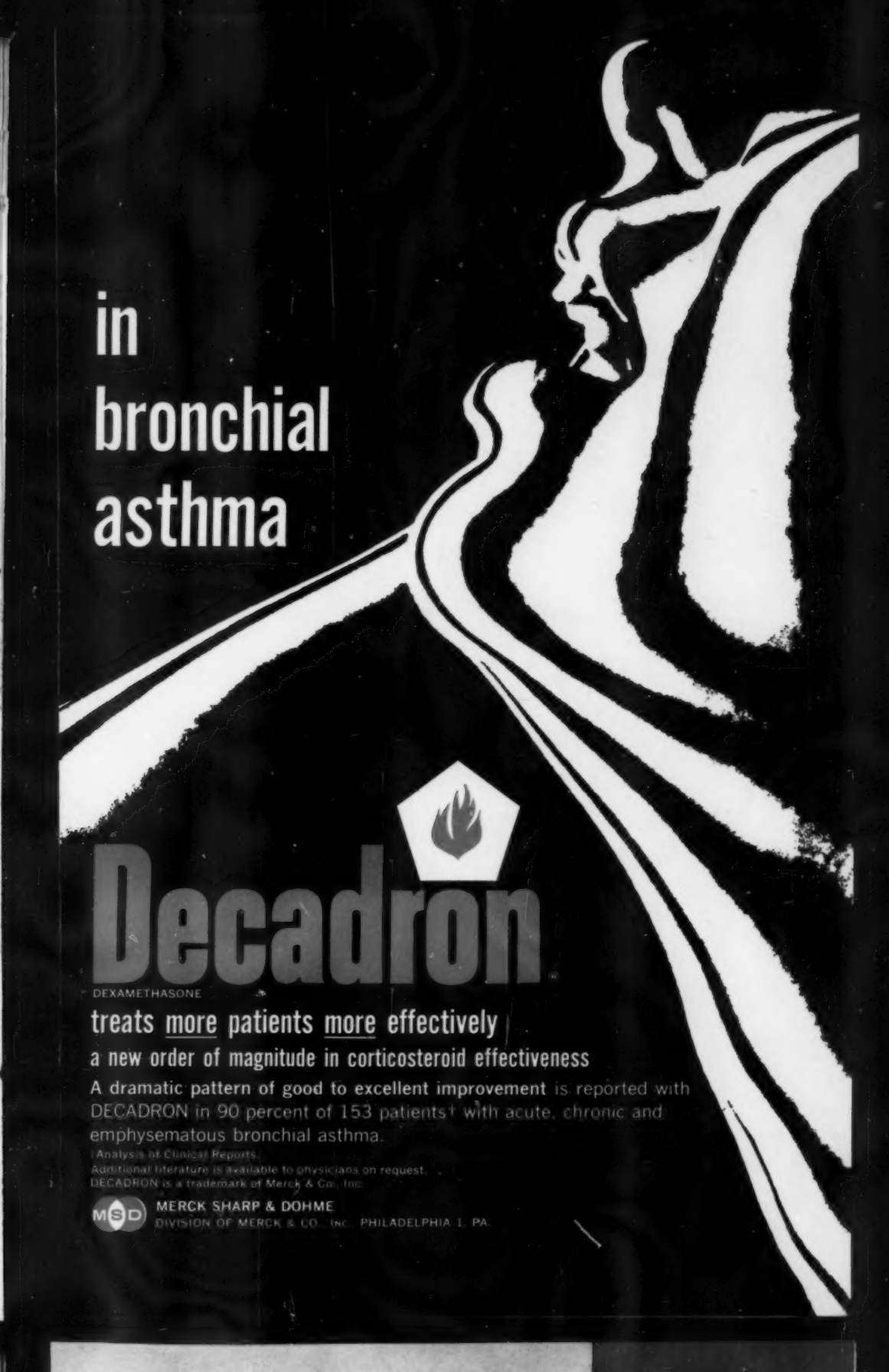
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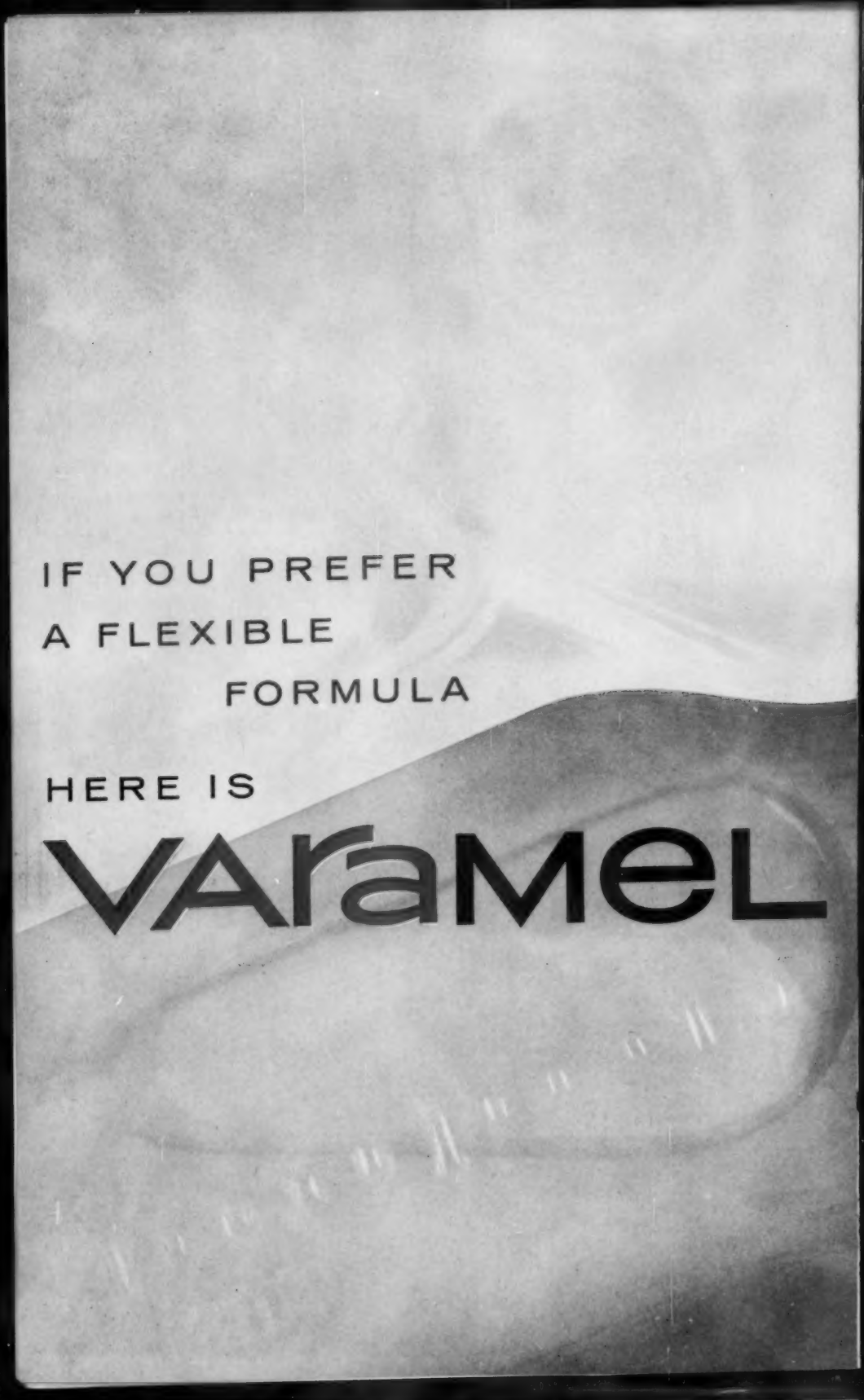
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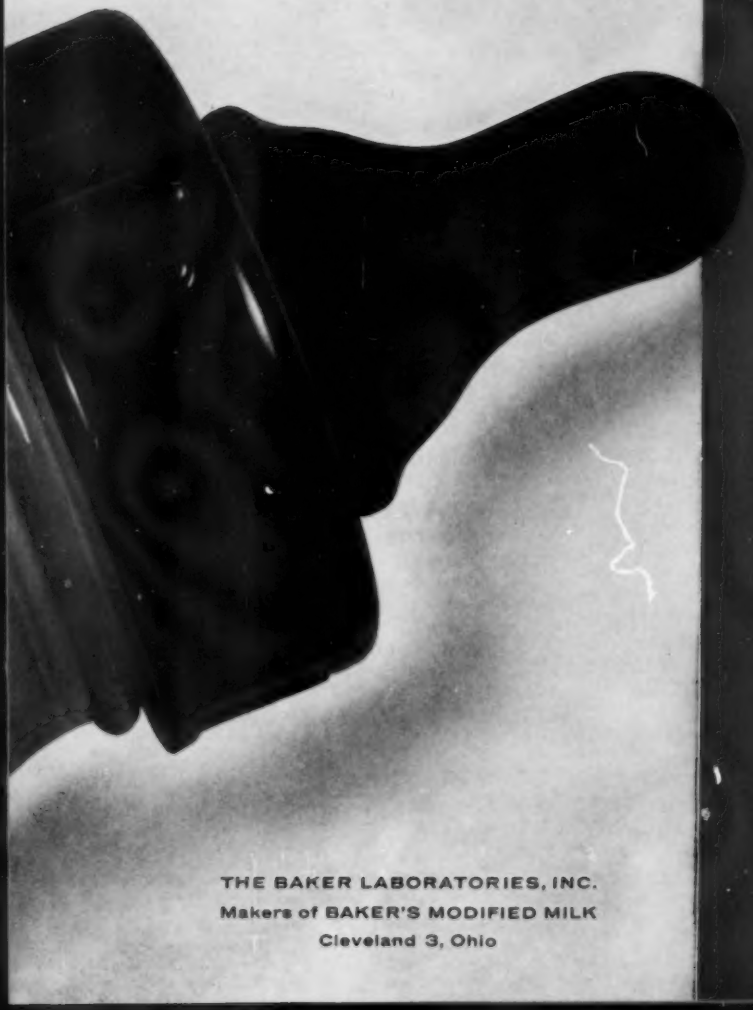

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Fatal Cardiovascular Collapse of Infants Receiving Large Amounts of Chloramphenicol

JAMES M. SUTHERLAND, M.D., Cincinnati

Death of three newborn infants (without obvious immediate cause of death at necropsy) followed administration of moderately large amounts of chloramphenicol. The recommended intramuscular dose of the microcrystalline suspension of chloramphenicol in aqueous vehicle was 100 to 150 mg. per kilogram of body weight per day for children of 15 kg. or less.[1-3] One death occurred after administration of 220 mg. per kilogram per day for 60 hours. Another death occurred after administration of 230 mg. per kilogram per day for 72 hours. The recommended oral dose of the suspension of chloramphenicol palmitate for children of 15 kg. or less was 50 to 100 mg. per kilogram per day[4] up to 100 to 150 mg. per kg. per day.[3,5] One death occurred after 50 mg. per kilogram per day for 56 hours and 10 hours after a single inadvertent oral dose of 400 mg.

The use of doses of chloramphenicol of the size recorded here has not been reported previously in newborn infants, and there has been little opportunity to observe possible adverse effects of such large amounts. Because of the wide antibacterial spectrum of chloramphenicol, the drug has been extremely useful. It is considered to be well tolerated and nontoxic, at least over short periods of time. Report of these possible adverse results of chloramphenicol therapy may permit other more definitive and better-controlled observations and indirectly result in a more rational application of a useful chemotherapeutic agent to the newborn infant with bacterial infection.

Submitted for publication Jan. 31, 1959.

Supported in part by a research grant from the National Institutes of Health, U. S. Public Health Service.

From the Departments of Pediatrics and Obstetrics, University of Cincinnati, the Children's Hospital Research Foundation, and the Laboratory for Study of Infant and Maternal Health.

Report of Cases

CASE 1.—The infant was a 3,440 gm. boy, born of a 33-year-old white married Gr. V, Group A, Rh+ mother with negative serologic test for syphilis at 40 weeks' gestation. During pregnancy the mother had a blood pressure of 140/80, and complained of edema and visual disturbances. Two previous pregnancies had resulted in spontaneous abortions at 12 and 6 weeks. The first two pregnancies terminated at 40 weeks with delivery of normal infants.

By history, membranes ruptured one week before delivery. The infant was delivered spontaneously by cephalic presentation 20 minutes after 100 mg. of meperidine (Demerol) hydrochloride, 1 mg. of levallorphan tartrate (Lorfan), and 1/150 grain (0.4 mg.) of scopolamine, and 4½ hours after onset of labor. Agar score was 10.

Initial examination of the infant revealed no abnormalities. Menadione sodium bisulfite, 5 mg., was given, and, because of the premature rupture of the maternal membranes, 50,000 units of procaine penicillin and 50 mg. of streptomycin intramuscularly every 12 hours were ordered. At 8 to 10 hours of age the infant went to breast and fed well. On the second day he was circumcised.

At 3 days of age, jaundice was noted and there was periumbilical erythema which extended in a

triangular area above the umbilicus. Rectal temperature was 99 F. The infant was nursing well. Blood was drawn for culture and subsequently grew no organisms. The streptomycin was discontinued, and 250 mg. of chloramphenicol every eight hours intramuscularly was started. At 6 days the infant refused to nurse and was unresponsive, sallow, and pale. Rectal temperature was below 94 F. Respiration was shallow and rapid and without retractions. The lungs were clear to auscultation, and no murmurs were heard. The liver was slightly enlarged. The fontanelle was full.

The chloramphenicol was decreased; erythromycin was added, but the infant died at 7 days of age, 12 hours after the onset of signs of collapse and 60 hours (8 doses) after the initiation of chloramphenicol at 220 mg. per kilogram per day or 100 mg. per pound per day.

At autopsy no infection or jaundice was apparent. The right lung weighed 26 gm. and the left 21 gm. Lower lobes seemed consolidated; however, there was no gross evidence of edema or pus. Microscopically no explanation for death was found. The lungs showed diffuse atelectasis with aspiration of squamous cells and mononuclear foreign-body response.

On more careful examination of sections other changes were noted which were minor. These would usually have been overlooked and apparently did not result in death. There was slight neuronal necrosis; cardiac muscle fibers appeared of poor quality, and there was a diffuse increase in cardiac glycogen, but no focal cardiac necrosis was noted. The liver was congested and there were rare areas of focal necrosis. The spleen was congested, and the adrenals were normal. No bone-marrow changes were seen.

Case 2.—The patient was a 3,320 gm. infant born of a Negro, married, Group A, Rh-positive, primipara with negative serologic test for syphilis at 44 weeks' gestation. The mother had had no prenatal care and was admitted in labor with albuminuria and a systolic blood pressure over 200 mm. Hg.

After a five-and-one-half hour labor with no medication the infant was delivered by vertex presentation under nitrous-oxide and oxygen anesthesia with a mediolateral episiotomy. At birth the infant had an Apgar score of 6 and was noted to be meconium stained.

A foul odor was encountered on physical examination. The time of rupture of the maternal membranes was unknown, and 50,000 units of procaine penicillin and 250 mg. of chloramphenicol were started intramuscularly every eight hours. Menadione sodium bisulfite 5 mg. was given. At 8 hours the infant nursed at the breast. At 2 days rectal temparature was 99 F. The infant did not seem ill and he was circumcised.

At 4 days of age the infant developed a gray color and a cold moist skin in spite of a temperature of 99 F. The infant died at 106 hours of age, 8 hours after the onset of vascular collapse. He had received 250 mg. of chloramphenicol 9 times in 72 hours, or 230 mg. per kilogram.

At postmortem examination the lungs weighed 40 gm., and there was lobular consolidation. The heart weighed 21 gm. and was moderately dilated. On microscopic examination there was patchy atelectasis and emphysema without an apparent causative factor. There was a trivial pneumonitis. Quite extensive focal myocardial degeneration with pyknosis was seen. There was some vacuolization of proximal renal tubules. No bone-marrow changes were noted.

Case 3.—The patient was a 3,200 gm. infant girl born by elective repeat section of a white, married, Gravida II, Para I, Rh-negative mother with a negative indirect Coombs test and negative serologic test for syphilis.

The mother's first pregnancy resulted in a pelvic delivery of a normal infant. The second pregnancy was terminated after a diagnosis of abruptio placentae by a cesarean section delivery of a normal infant who was blood group O, Rh-negative, with a negative direct Coombs test. The white count was 29,300 per cubic millimeter of blood with 63% segmented neutrophils, 4% young neutrophils, 1% basophils, 25% lymphocytes, and 7% monocytes. There were 4 nucleated red blood cells per 100 white cells.

At one day of age the infant's abdomen was distended, though gas was passed per rectum. Roentgenograms of the chest and abdomen were interpreted as normal. Procaine penicillin, 50,000 units, and 25 mg. of streptomycin were started twice daily. The abdominal distention was still noted at 2 days but by 3 days of age was absent. At 4 days the nurses noted that the infant was a "poor eater." The streptomycin was discontinued, and 50 mg. of chloramphenicol palmitate orally every 8 hours was started. The infant continued to feed poorly.

At 8 p. m. on the sixth day of life and after 7 doses of 50 mg. of chloramphenicol, or 350 mg. in 56 hours (50 mg. per kilogram per day), 15 cc. of chloramphenical palmitate (400 mg.) was given. Three hours later the infant was pale, and the abdomen was distended. Temperature was 96 F. There was generalized cyanosis more marked in dependent areas. The peripheral pulse was 80 to 100 and weak. Generalized flaccidity was present. An enema was given. Roentgenograms of the abdomen showed distention with gas, but no evidence of ileus or obstruction. Hemoglobin was 14.5 gm. %. Another white count revealed 40,700 white blood cells per cubic millimeter with 39% segmented neutrophiles, 3% stab forms, 1% eosinophils, 54% lymphocytes, and 3% monocytes. A

blood culture was drawn and subsequently grew no organisms. A lumbar puncture revealed no cells and culture was negative. The CSF protein was 131 mg. %, and the sugar (Somogyi-Nelson) was 180.5 mg. %. A simultaneous blood sugar of 2,160 mg. % had to be diluted 8 times before a spectrophotometer reading could be made.

After intravenous fluids with hydrocortisone, norepinephrine, penicillin, and chloramphenicol, the infant's color and condition improved for 20-30 minutes, but subsequently deteriorated again, and the infant died at the age of 7 days and about 10 hours after the large oral dose of chloramphenicol palmitate.

Necropsy revealed no obvious and immediate cause of death. Aspirated amniotic sac contents were present in the lungs with a minor degree of hemorrhage and edema. Lung cultures revealed no growth. There was a small tentorial tear; however, the only evidence of bleeding was a small hemosiderin stain. A rare small focus of subarachnoid blood was seen posteriorly. Abundant cerebrospinal fluid was encountered, but there were well-developed convolutional patterns and there was no dilatation of the ventricular system. The liver was enlarged and some fatty change was seen. The heart was enlarged, and there was a dilated left ventricle. No bone marrow changes were noted.

These three infants died with a clinical picture of vascular collapse. Two of the three were hypothermic. All three received doses of chloramphenicol significantly larger than are usually administered. There were no recognized pathological changes common to the three infants. Significant infection did not seem to be present at postmortem examination in any of the three infants.

Any of the three unexplained infant deaths at 5 to 7 days of age might have been overlooked. However, death in the only three infants who to our knowledge had received doses of chloramphenicol of this magnitude prompted a review of previous experience.

Comment

The absence of postmortem findings indicating any but minimal or subsiding infection in these three patients increases the likelihood that their deaths resulted from adverse drug action, although a clinical picture of vasomotor collapse and hypothermia may be associated terminally with overwhelming infections in the newborn infant.[6]

A review of the literature reveals only two patients who received such large doses of chloramphenicol. These patients, treated for typhoid with oral chloramphenicol of British origin, died with vasomotor collapse.[7] One patient was a 40 kg. woman who received 14 gm. of chloramphenicol in 36 hours (about 230 mg. per kilogram per day). The other patient was a 25 kg. girl who received 17 gm. of chloramphenicol in 60 hours (about 280 mg. per kilogram per day). On a weight basis, the doses received by these two patients are similar to the amounts received by the reported infants. Death of these two typhoid patients cannot be ascribed to the large doses of chloramphenicol alone, for a similar picture of peripheral vascular callopse has been seen in typhoid treated with chloramphenicol orally administered in smaller dosage and produced in various countries.[8-24] In some of the reported patients the drug was discontinued and the patients improved and survived.[12,14] In others, vasomotor collapse terminated in death[10,11,23] with none of the postmortem changes of acute fatal typhoid.[16,19] In still others, a milder and apparently reversible vasomotor collapse occurred even though the drug was not discontinued.[8,15,23] Florey[25] stated that collapse was not seen in typhoid before the introduction of chloramphenicol; however, antipyretics are said to be contraindicated in typhoid,[26,27] because hypothermia and vascular collapse may occur.[28] Certainly, severe vascular collapse has not been recognized as a frequent complication of thypoid fever unless there is perforation, hemorrhage, or myocarditis. Shapiro[29] and co-workers stated deaths of chloramphenicol-treated typhoid patients resulted from the severity of the illness and lowered patient resistance. Mollaret et al.[16] ascribed the adverse effect of chloramphenicol in typhoid to rapid destruction of bacteria and release of bacterial endotoxin. He demonstrated that guinea pigs inoculated with Salmonella paratyphi *B*

and treated with chloramphenicol died in 18 to 24 hours while the untreated, uninoculated animals survived 8 to 10 days. Control animals who received only chloramphenicol did not die. Farinaud and Portes,[20] in the treatment of typhoid, reported no vasomotor collapse when they used small amounts of chloramphenicol initially and gradually increased the dosage. A similar situation was observed in treatment of Brucella melitensis infection with chlortetracycline (Aureomycin).[30] No adverse reaction was noted in patients receiving smaller doses of the drug, whereas transient peripheral vascular collapse occurred on larger doses. It is remotely possible that the infants reported in this paper were infected with micro-organisms responsive to chloramphenicol, but that the large doses resulted in rapid bacterial destruction and the collapse was caused by toxic bacterial products.

Vasomotor collapse apparently can occur during administration of chloramphenicol in the absence of bacterial infection.[24] For example, anaphylactoid reactions following chloramphenicol occur, but they have been described only twice. One patient,[31] a nurse, developed hypotension, a weak and thready pulse with cold moist skin. She responded to artificial respiration epinephrine, oxygen, and cortisone. The other patient[32] noted onset of pruritus 30 minutes after ingestion of the first dose and in a few minutes developed angioneurotic edema with laryngeal involvement. Blood pressure was unobtainable. He was treated with aminophylline, diphenhydramine (Benadryl), epinephrine, and supportive therapy, and was well in a few days. None of the three infants reported here clearly present any findings suggesting an allergic component to their collapse.

The gray pallor in the three infants raised the question of methemoglobinemia. This phenomenon is unlikely, for, although determinations of methemoglobin were not done, the three infants did not show the characteristic slate cyanosis, chocolate-colored blood or tissues either during life or at necropsy.

Cramer and Rossi[33] reported two children under 3 years of age who died with collapse after vomiting and diarrhea during the course of oral chloramphenicol therapy. In these two patients, there was alteration of the body and particularly bowel flora by resistant organisms (staphylococci). Two of the three infants reported here received parenteral chloramphenicol, and the effect on bowel flora would be limited.[34] There was no evidence in any of the three of acute, progressive, local or generalized infection.

The fact that the three patients are all newborn infants raises the question of peculiar response of the newborn animal and perhaps indeed only the newborn human animal to this drug. Acute toxicity studies limited to adult animals have revealed a fair degree of tolerance.[35] An L. $D._{50}$ of 275 mg. per kilogram administered subcutaneously to mice in chronic toxicity studies of two weeks' duration was reported. An acute L. $D._{50}$ was not reported for intramuscularly or subcutaneously administered chloramphenicol. "Lethal or near lethal amounts of chloramphenicol orally and parenterally caused acute respiratory depression or failure, accompanied by fall of blood pressure and anoxia."

Microbiologic assays of chloramphenicol, which predominantly determine the unconjugated or active fraction of chloramphenicol,[36] reveal no particular elevation in the blood of infants after oral medication. Larger oral doses are probably required in the newborn to achieve comparable microbiologic blood levels than at an older age,[37-42] although it is difficult to compare the patients and assay methods of one author with those of another. There are very few data on the levels which can be achieved by the intramuscular route in newborn infants.[43,44] Perhaps absorption from the muscular depot differs from the young patient to the older patient, or perhaps the newborn eliminates the drug poorly and a stepladder increase occurs with each ad-

ditional dose, as the data of Ross et al. suggest.[45,46]

A failure to conjugate and hence excrete chloramphenicol is possible, for in adult human urine 90% of the excreted chloramphenicol appears as the inactive glucuronide.[47,48] The enzyme necessary for this conjugation is decreased in newborn animals[49] and may be decreased in newborn humans. An inability to form a glucuronide might result in an alternate and more toxic metabolite. The glucuronide mechanism is not however, the only fetal or infant metabolic pathway which differs from that of the older person.[50]

Both Viti[24] and Groh[51] suggested that chloramphenicol had an effect on carbohydrate metabolism. The extremely high blood sugar observed in Case 3 might have been disregarded as a laboratory or sampling error. However, an elevated blood sugar of 175 mg. % was observed in an 8-month infant during collapse after three days of therapy with multiple drugs, including chloramphenicol, for staphylococcal pneumonia.

Groh demonstrated that repeated two-dose glucose tolerance tests (Staub-Traugott) during the course of 15-day treatment of infants with oral chloramphenicol revealed delayed glucose breakdown. This change did not occur when oral B vitamins were administered simultaneously. The carbohydrate effect of chloramphenicol was ascribed to a decrease in production of B vitamins (coenzymes) in the gastrointestinal tract.

In contrast, Viti described fasting hypoglycemia (Hagedorn-Jensen method) in normal adults after 5 days of oral chloramphenicol therapy, more marked after 10 days of therapy, with return to normal 10 days after discontinuation of the drug. He attributed the vasomotor collapse observed in chloramphenicol therapy to hypoglycemia. At present there is no information which permits conclusions applicable to the infants here from these two dissimilar groups of patients studied in different manners.

Other authors[22] have suggested that chloramphenicol has its primary acute toxic effect on the autonomic nervous system.

It is possible that the chloramphenicol used in other countries may not be made under license by the American manufacturer and may be dissimilar from the American product. However, many of the adverse reactions have been described with drugs from countries where license of the American manufacturer would be expected. It also could be argued that this possible acute toxicity could be altered by changing the acid in the ester. It is unlikely that changing the acid[46,52] could qualitatively alter the possible acute toxic effect of chloramphenicol, for two of the infants reported here received the microcrystalline suspension and one received the palmitic acid ester. Alteration of the acid to increase efficiency of absorption[46] would probably increase toxicity.

It is surprising that the acute adverse effects of chloramphenicol, whatever their cause, are so well known in other countries and so seldom recognized in this country.

Summary

Death of three newborn infants with peripheral vascular collapse occurred after large doses of chloramphenicol were administered intramuscularly to two infants and orally to a third infant. The adverse effect of doses of chloramphenicol of one and a half recommended amounts might result from any one or more of the following factors, some of which have been suggested previously: (1) rapid destruction of bacteria and release of endotoxin; (2) drug hypersensitivity; (3) methemoglobin production; (4) overgrowth of resistant organisms; (5) toxic alternate metabolites; (6) efficient absorption and/or poor elimination of drug; (7) hypoglycemia; (8) disturbed carbohydrate utilization, and (9) adverse effect on autonomic nervous system.

On the basis of the three patients reported it is not possible to ascribe an adverse effect to the drug in recommended amounts. The

three deaths are reported in the hope of stimulating publication of the observations of others which may lead to less tentative conclusions than are possible on the basis of a few uncontrolled case reports.

Miss Jane Becker, Drs. William Schubert, William Margaretten, Stanley Graven, Ralph Tierney, and A. F. Michael aided in assembling material on these and other patients, and Dr. Benjamin H. Landing interpreted the gross and microscopic autopsy findings.

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Congenital Asymmetry, Short Stature, and Elevated Urinary Gonadotropin

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In 1953 we[1] first described the "Syndrome of Congenital Hemihypertrophy, Shortness of Stature, and Elevated Urinary Gonadotropins" in two children, a girl aged 5½ years and a boy 6 years old. Subsequently Silver and Gruskay[2] reported a case of hemihypertrophy and elevated urinary gonadotropin in a 7-year-old boy with normal height. In none of these cases was there any other evidence of apparent endocrine disturbance. The purpose of this paper is to report two additional cases of this syndrome: the first in an 8½-year-old Negro boy with shortness of stature and elevated urinary gonadotropins in whom the difference in the two sides of the body was limited to the spine, and the other in an 8-month-old white boy with shortness of stature, a difference in size of the legs, and swelling of the dorsa of the hands and feet. A tabulation of the findings in these five cases is presented.

Report of Cases

CASE 1.—A Negro boy was first seen in the New Haven Hospital Pediatric Out-Patient Clinic at the age of 8½ years because of shortness of stature. He had been born four days before the expected day of delivery and had been 19 in. long, but had weighed only 1,650 gm. (3 lb. 10 oz.). At the beginning of the second trimester of the pregnancy the mother had been operated upon and a 1,365 gm. (3 lb.) "fibroid tumor of the ovary" removed. She had otherwise been well during the pregnancy. The patient had appeared normal at birth except for his exceedingly thin appearance. He weighed only 2,275 gm. (5 lb.) at one month and 3,640 gm. (8 lb.) at six months, when scoliosis was first noted. The mother thought that the right leg and arm appeared longer and larger than the left.

Submitted for publication Dec. 16, 1958.

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He had received supplemental vitamins continuously during infancy, and these had been continued intermittently since then. As an infant he had vomited easily, and the mother reported that during the first two or three years of life he had had difficulty in chewing foods so that they would be fine enough to swallow.

The patient was an only child. The mother was 31 years old and well. She had had pulmonary tuberculosis, but the disease was said to have been arrested three years prior to the birth of the patient. She was 161 cm. (5 ft. 3¼ in.) tall. The father was 31 years old and well. He was 170 cm. (5 ft. 7 in.) tall. The family history otherwise was negative. There had been no unusually short members in either branch of the family, nor had any member of the family had asymmetry.

Gross motor development had been slow during infancy (influenced in part by the scoliosis) and mental development had always been retarded. He did not sit without support until the age of 24 months. He walked without support at 26 months of age. He was enrolled in a special class in school and was doing kindergarten work at 8½ years. Deciduous and permanent dentition was said to have been normal.

System review was not contributory. He had previously complained of back pains, but this had not been present for the preceding two or three years. No symptoms suggestive of endocrine disturbances were elicited.

Physical Examination: He was a short, slender boy who looked and acted more like a 6-year-old than his chronologic age of 8½ years (Fig. 1, *A*). He was 110 cm. (43½ in.) tall, (50 percentile for 5 years) and weighed 16.4 kg. (36 lb.) (50 percentile for 4 years). Head circumference was 48 cm. (19 in.). There were several areas of darker pigmentation on the lower back which were suggestive of café au lait spots. The dental age was consistent with the chronologic age, but there was poor alignment of the teeth, the permanent lower lateral incisors having erupted behind the central incisors. The genitalia were normal. Both testes were descended and of normal size. The lengths of both upper and lower extremities were bilaterally equal. The little fingers were short and curved inward (Fig. 2, *A*). There was marked

Fig. 1.—*A*, Present Case 1, with congenital asymmetry of spine, shortness of stature, and elevated urinary gonadotropin. *B*, Present Case 2, with congenital asymmetry of extremities and shortness of stature. Note the inverted "V" mouth and relative hypoplasia of the mandible. *C*, Case 1 of Silver et al.,[1] with congenital hemihypertrophy, shortness of stature, and elevated urinary gonadotropin. Note the difference in size of the arms and legs. *D*, Case 2 of Silver et al.,[1] with congenital hemihypertrophy, shortness of stature, and elevated urinary gonadotropin. Note the inverted "V" mouth and relative hypoplasia of the mandible. *E*, Silver and Gruskay's[2] case, with congenital asymmetry of the extremities, average height, and elevated urinary gonadotropin.

Fig. 2.—Incurving of the little finger of patients with congenital asymmetry and shortness of stature. *A*, Present Case 1. *B*, Present Case 2. Note the swelling of the dorsum of the hand. *C*, Case 2 of Silver et al.[1]

deformity of the spine, with prominence of the right scapular area. The right shoulder was 1 cm. higher than the left. When he stood erect, there was scoliosis in the lower dorsal region with convexity to the right and considerable scoliosis in the upper lumbar region with the convexity to the left. When he bent forward, the right spacular area was appreciably more prominent than the left.

Roentgenograms of the spine showed a kyphoscoliosis in the mid-dorsal area with lateral and anterior wedging of the bodies of the fifth, sixth, seventh, and eighth dorsal vertebrae (?hemivertebrae) and apparent fusion of the second, third, and fourth dorsal vertebrae (Fig. 3). The wedging might have been due to retarded development of the secondary ossification centers. There was irregularity of the growth centers of the superior and inferior surfaces of T5, 6, 7 and 8 on the left side (?osteochondrodystrophy) and rotation and reduction in the laterovertical diameter of the centra (Fig. 3).

Epiphyseal maturation at the age of 6 years 5 months had been 3 years 8 months, while at the age of 7 years 8 months his "bone age" was 4 years. Roentgenograms of the skull were normal. Ophthalmological examination was noncontributory.

Routine blood count and urinalysis were normal. Serum cholesterol and alkaline phosphatase were also within normal limits. A 24-hour urine sample was collected and assayed for gonadotropins. It was positive for 4.5 and negative for 9.0 mouse uterine units per 24 hours of urine.

Case 2.—A white boy was first seen at the University of Colorado Medical Center at the age of 6 months because of shortness of stature. He had been born two weeks after the expected day of delivery but had weighed only 2,430 gm. (5 lb. 6 oz.). At the end of the first trimester of pregnancy the mother had had moderately severe Asian influenza but had otherwise been well during the pregnancy. The patient had appeared normal at birth, but during the neonatal period it was noted that he ate poorly, never appeared to be hungry, and was "very sleepy." At 3 weeks of age he weighed only 2,620 gm. (5 lb. 12 oz.). He had been well except for an episode of "congestion of the lungs" at the age of 5 months, at which time he had been hospitalized

Fig. 3.—Roentgenograms of spine in present Case 1. *A*, Full spine. *B*, Close-up of thoracic spine.

and had responded promptly to antibiotic therapy. When he was about one month old, the parents had noted that the right foot was not as large as the left, and the difference in size was subsequently also noted to involve the right leg.

The patient was the fourth child of parents who were both 32 years old. The parents and three older siblings exhibited no significant asymmetries and were of normal size. However, a paternal niece and nephew were said to be "very small."

Physical Examination: He was a short, slender infant who looked younger than his chronologic age of 6 months (Fig. 1, *B*). He was 58 cm. (22¾ in.) tall (50 percentile for 2 months), weighed 4,510 gm. (9 lb. 15 oz.) (50 percentile for 7 weeks), and had a head circumference of 45 cm. (17¾ in.). There was a single oval area of darker pigmentation measuring 3×5 mm. over the dorsum of the left wrist. The anterior fontanel was 0.25 cm. in size. The occiput was prominent. The outer angles of the mouth were drawn down, producing an inverted "V." No teeth had erupted. There was some increase of skin of the back of the neck. The nipples were widely spaced but of normal size. The penis was of normal size, but there was a slight chordee and neither testes could be palpated in the scrotum. There was moderate cubitus valgus of the arms. The dorsa of both hands and feet were puffy but did not "pit" on pressure. The right foot was approximately 0.4 cm. smaller than the left and the right leg 0.5 cm. shorter than the left. The fifth fingers of both hands were curved inward but not short (Fig. 2, *B*). The second toe on the right foot was curved and longer than the first toe. Both ankle and hip joints were very mobile. He could reach and pick up objects and roll over but was unable to sit alone. Epiphyseal development was said to be "delayed."

On reexamination at the age of 8 months he weighed 10 lb. 4 oz. and was 24 in. long. The physical findings previously noted were essentially unchanged except that the difference in size between the right and the left leg was more marked than on the previous examination.

There was an absence of sex chromatin in cells studied from the mucous membrane of the mouth.

Comment

Slight differences in size between the two sides of the human body are so common that they are not considered to be significant. Marked asymmetries with hemihypertrophy are relatively rare, and there are less than 130 cases reported in the literature.* The asymmetry can be partial or total as well as crossed. It may be "true," involving the skeleton as well as the soft tissues of the body, or "pseudo," without involvement of bony structures. In certain instances it is exceedingly difficult to determine whether the asymmetry is due to hypertrophy of one side or atrophy of the other. The first patient herein reported had asymmetry of the spine, shortness of stature, and abnormally small birth weight, despite a history of having been born at full term, a pregnancy complicated by the removal of a 3 lb. "fibroid of the ovary" during the fourth month, delayed epiphyseal maturation, incurved little fingers, and elevated urinary gonadotropins *for the age*. The second patient had shortness of stature, a difference in size of the two legs, drawing down of the corners of the mouth, and small birth weight, despite the history of being born two weeks after the expected day of delivery, a single café au lait spot, nonpitting swelling of the dorsa of both hands and feet, incurving of the fifth fingers, moderate cubitus valgus, a slight increase in the amount of skin on the back of the neck, and cryptorchidism.

A review of these patients and of the three similar cases previously reported reveals that the urinary gonadotropins were elevated for the age in all four cases in whom this test could be performed, being positive at 4.5, 5.0, 5.0, and 35.2 mouse uterine units, respectively (Table). In our laboratory, normal women during the reproductive period of life have been found to excrete more than 5.0 and less than 52 mouse uterine units, and all normal children under 9 years who have been tested have been found to excrete less than 2 mouse uterine units per 24 hours.

Congenital hemihypertrophy or marked asymmetry was present in all five patients. The asymmetry involved the entire body in two patients, the extremities in two, and was limited to the spine in the fifth. Shortness of stature occurred in four of the five patients. In three of these it was marked.

* For a review of the subject of hemihypertrophy the reader is referred to the previous articles in this series[1,2] and to the article by Ward and Lerner.[3]

Tabulation of Findings in the Syndrome of Congenital Asymmetry (Hemihypertrophy), Shortness of Stature, and Elevated Urinary Gonadotropins

	Case 1	Case 2	Case 3 *	Case 4 †	Case 5 ‡	Incidence, %
Urinary gonadotropins	Elevated	Not performed	Elevated	Elevated	Elevated	100 §
Congenital hemihypertrophy or marked asymmetry	Present (spine)	Present (extremities)	Present (entire body)	Present (entire body)	Present (extremities)	100
Shortness of stature	Present	Present	Present	Present	Absent	80
Birth weight (at full term) abnormally low	Yes	Yes	Yes	Yes	No	80
Difficulties during pregnancy	Present	Present	Present	Present	Absent	80
Café au lait mark of skin	Present	Present	Present	Absent	Present	80
Fifth finger						
(a) Shortened	Yes	No	No	Yes	Yes	60
(b) In-curved	Yes	Yes	No	Yes	No	60
"Bone age"	Delayed	"Delayed"	Normal	Normal	Delayed	60
"Bone age" on two sides of body	Same	Not known	Same	Different	Different	50
Inverted "V" or "shark mouth"	Absent	Present	Absent	Present	Absent	40

* Silver et al.[1] Case 1.
† Silver et al.[1] Case 2.
‡ Silver and Gruskay's[1] Case.
§ Performed in only 4 of the 5 patients.

All five children were supposedly born at or after full term but in four the birth weight was only 3 lb. 10 oz., 3 lb. 12 oz., 4 lb., and 5 lb. 6 oz., respectively. The pregnancy was complicated in four of the five cases. In one the mother had had several episodes of abdominal pain and vomiting as a result of "gallbladder disease"; in another the mother had been in an automobile accident during the seventh month of pregnancy, and this had been followed by a cessation in weight gain until the delivery of her child; in the third a "fibroid tumor of the ovary" weighing 3 lb. had been removed at the beginning of the second trimester; while in the fourth the mother had had moderately severe Asian influenza at the end of the first trimester. Café au lait spots were present in four of the five children. In three the fifth fingers of both hands were unusually short and in 3 the fifth finger had a marked incurve.

Epiphyseal maturation ("bone age") was delayed in three cases and normal in the other two. In one case with normal epiphyseal development and in one in whom the "bone age" was delayed, there was a difference in maturation between the two sides of the body.

Two children had a peculiarity of their mouths. The outer angles were drawn down, producing an inverted "V" or "shark mouth." Russell[4] has called attention to this finding in patients he has described with shortness of stature, small size at birth, and incurved little fingers. In two of his patients a disproportion existed in the two sides of the body. Unfortunately, assays for urinary gonadotropins were not reported in Russell's patients.

No correlation seemed to exist between the syndrome as seen in these five cases and any of the following factors: sex, race, family history, mental development, dentition, or genital development. The structure of the skeleton (by roentgenogram) was normal in all cases. The protein-bound iodine and urinary 17-ketosteroids were normal in the two cases in whom these determinations were performed.

Silver et al. have suggested that the pathogenesis of the condition herein described may be similar to that which occurs in patients with gonadal dysgenesis. In the latter condition it has been found that the majority of cases have a sex chromatin pattern that is characteristic of males even though they may have the outward appearance of immature females. Unfortunately, the only female with the syndrome of congenital asymmetry, shortness of stature, and elevated urinary gonadotropins was studied

before this test was available to us and we were unable to determine whether an abnormal chromatin pattern was present. In Case 2 of the present report, the findings of slight webbing of the neck, moderate cubitus valgus, swelling of the dorsa of the hands and feet, and wide spacing of the nipples were all suggestive of gonadal dysgenesis. However, exploratory laparotomy was not performed, and assay of urine for gonadotropin could not be carried out.

Summary

The fourth case of the syndrome of congenital asymmetry of the body, shortness of stature, and elevated urinary gonadotropins is reported in an 8½-year-old boy.

A fifth case with shortness of stature and a difference in size of the legs is described, in whom certain signs suggestive of gonadal dysgenesis were also present.

A tabulation of the findings in patients with this syndrome is presented.

Dr. Milton J. E. Senn, Professor of Pediatrics, Yale University School of Medicine, New Haven, gave permission to report Case 1.

4200 E. 9th Ave. (20).

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Pulmonary Ventilation in Infants Under One Year of Age

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Measurement of pulmonary ventilation in infants has been performed by a number of investigators.[1-8] In the last three decades plethysmographic methods have been used by most groups, although it has recently been demonstrated that the mask-and-bag technique is possible in small infants.[7,8] Observations have been chiefly limited to the newborn period, although one study has included a few infants up to 3 months of age.[2] None of the studies to date have included data on flow rates.

The purpose of this paper is to describe a method which permits direct measurement of ventilation. In addition, observations which have been extended to infants up to 8.9 months of age are included.

Submitted for publication Oct. 22, 1958.

From the Department of Pediatrics, The Ohio State University, and The Children's Hospital.

Supported in part by grants from the National Foundation for Infantile Paralysis, The Ross Laboratories, and The Central Ohio Heart Association.

Methods

The apparatus (Fig. 1) employs the bag-in-box principle. The box is constructed of Lucite, is airtight, and has a 27 liter capacity. Within the box is a Neoprene balloon of 6 liter capacity. The box and the bag are separately connected by rubber tubing and one-way low-resistance J-valves * to an infant anesthesia mask in which Plasticine is incorporated to reduce the dead space to less than 10 ml. The subject breathes from the box into the balloon. Opposite the entry of the tubing is an opening in the box around which is sealed a high-compliance bellows constructed of thin vinyl film reinforced at the folds with x-ray film. With removal of air from the box or addition into the balloon there is excursion of the bellows. Firmly applied to the bellows is a Constantin wire strain gauge unit which is, in turn, connected thru a strain-gauge amplifier to a recording apparatus.† The strain-gauge unit consists of two Constantin wire strain gauges ‡ cemented to opposite sides of

* Obtained from Warren E. Collins, Inc., 555 Huntington Ave., Boston, Catalogue No. J-1.

† The recording apparatus used was a Sanborn Twin Viso Recorder, Model 60-1300, with a Sanborn Strain Gauge Amplifier, model 64-500-B.

‡ Baldwin SR-4, Type A-1, obtainable through Baldwin-Lima-Hamilton Corporation, 42 4th Ave., Waltham 54, Mass.

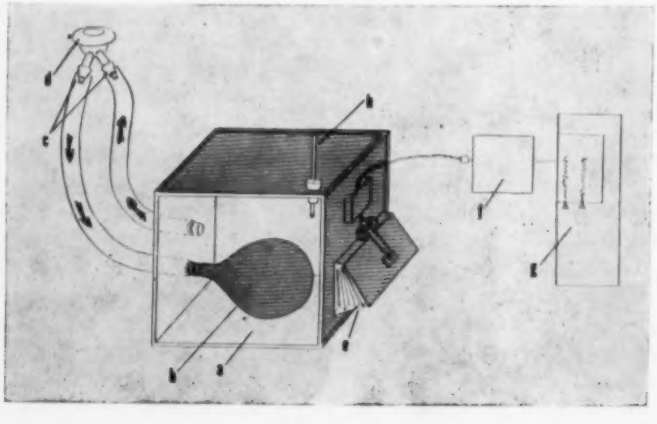

Fig. 1. — Diagram of apparatus used in ventilation studies. (*a*) Lucite box; (*b*) neoprene balloon; (*c*) tubing with one-way J-valves; (*d*) infant mask with dead space largely replaced by Plasticine; (*e*) vinyl film bellows with strain gauge; (*f*) strain-gauge amplifier; (*g*) recorder; (*h*) thermometer.

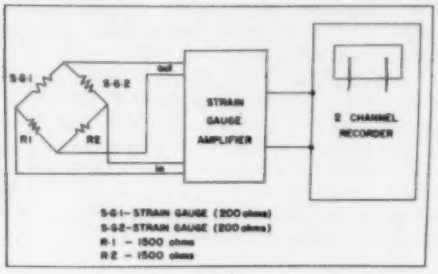

Figure 2

Fig. 2.—Strain-gauge circuit.

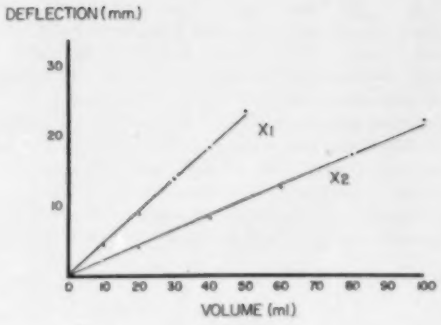

Figure 3

Fig. 3.—Calibration curves. Shown here are the calibrations when the recorder is unattenuated (X1) and at twofold attenuation (X2).

a 0.001 in. thick strip of brass. Flexible movements are localized to the most sensitive portions of the gauges by stiffening opposite ends of the gauges by windings of plastic tape. To minimize the effect of temperature on the gauge wire two gauges are employed, and these form adjacent arms of a Wheatstone bridge. Resistance changes due to temperature alone will be the same for both of the arms of the Wheatstone bridge. Thus, temperature effects on the gauges will have minimal effect on changes in resistance due to flexural movements of the gauges. A diagram of the circuit is shown in Figure 2. The use of the strain gauges and the circuitry was modified from the one described by Stewart, Grossman, and Kadetz.[9] Electrical amplification of the signal allows a full-scale deflection of the tracing with a 105 ml. volume. Single volumes up to 250 ml. may be recorded on the trace with attenuation of the signal. The recorder is run at a speed of 25 mm. per second, which spreads out the individual respiratory cycles and permits ready analysis of the various components of each cycle.

The spirometer is calibrated before and after each run with a 50 ml. Luer-Lock syringe. The calibration at full scale and at an attenuation of X2 is essentially linear (Fig. 3). When constant volumes are used, the rate at which air is added to or removed from the spirometer, i. e., the velocity of flow, has no effect on the excursion of the bellows.

A typical cycle is shown in Figure 4. Inspiration is downward. The vertical distance between beginning inspiration and the base line is equal to the tidal volume. Mean flow rate of inspiration or expiration is determined by measuring the distance of a perpendicular line 25 mm. from the apex of the angle made by the base line and the line connecting end inspiration with beginning inspiration or end expiration, respectively. Flow rates are thus measured in units of milliliters per second and are converted to liters per minute. Maximal rates of flow can be measured also but are not included in this report.

Temperature within the box is recorded before and after each collection, and all volumes are converted to BTPS (body temperature, ambient pressure, saturated with water).

Material

The infants in this study were selected from the well-baby clinics of the outpatient department.

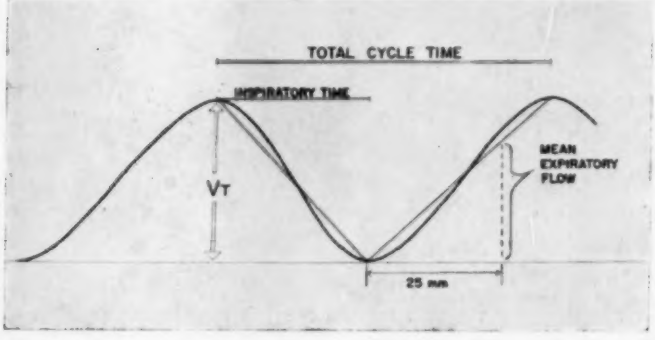

Fig. 4.—Diagram of a respiratory cycle. See text for procedure used in measuring flow rates.

All subjects had normal rectal temperature. Infants who were asleep when brought to the clinic were taken directly to the pulmonary laboratory and measurements attempted. Infants awake on arrival were fed, and those who fell asleep were subsequently measured. All infants were from 15 to 60 minutes post prandial. All were either asleep or very drowsy. Subjects were excluded from the study if there was evidence of physical activity or irregularity of the breathing pattern. In some instances a pacifier was placed in the mouth during the measurements of ventilation. This had no apparent effect on the tracing and succeeded in keeping patients either asleep or very drowsy. It is believed that all of the infants included in this study were in a steady state. In 48 of 100 infants the above criteria were satisfied. One infant, Case 8, had measurements on two successive days. In the majority of subjects, duplicate or triplicate observations were made with an interval of 5 to 20 minutes between runs. Each infant had a continuous recording of at least one minute.

TABLE 1.—*Ventilation Data on Forty-Eight Normal Infants*

Case No.	Age, Mo.	Weight, Lb.-Oz.	Surface		Vt, Ml.		I/T	Vol. L/Min.	Vol. L/Min/M.²	Flow Rate, L/Min.	
			Length, In.	Area, M²						Insp.	Exp.
1	2.2	10-15	23.0	0.27	48.1	53.6	.56	2.58	9.56	6.1	7.6
2	3.0	14	24.0	0.31	30.3	58.0	.42	1.76	5.68	5.6	4.1
3	0.2	8- 2	17.5	0.19	23.3	48.4	.30	1.13	5.95	6.5	4.5
4	3.6	12- 2	24.5	0.30	37.7	35.3	.46	1.11	3.70	3.2	2.5
5	2.9	9- 7	22.0	0.25	33.0	22.4	.29	0.74	2.95	3.6	1.2
6	1.7	9- 6	21.0	0.23	18.6	43.5	.48	0.81	3.53	2.5	2.6
7	5.9	16- 8	26.0	0.35	47.8	42.0	.44	2.01	5.74	6.8	4.3
8	0.7	10- 5	20.0	0.24	21.2	42.9	.49	0.91	3.78	2.7	2.4
					33.3	56.9	.51	1.90	7.92	5.3	5.2
.9	0.2	6-12	17.0	0.18	13.7	51.5	.47	0.70	3.92	2.1	2.1
10	5.1	14	24.0	0.31	46.1	43.4	.47	2.00	6.45	6.8	5.3
11	1.3	10-12	22.0	0.26	27.2	50.0	.53	1.36	5.23	3.5	4.3
12	1.0	9- 5	22.0	0.22	22.5	42.5	.45	0.95	4.32	3.2	2.3
13	3.1	14-10	24.5	0.32	26.6	54.5	.51	1.45	4.54	4.3	4.1
14	3.8	15- 4	25.0	0.36	34.5	30.7	.45	1.06	2.94	3.4	2.4
15	3.0	10- 1	24.0	0.27	28.7	39.3	.52	1.13	4.19	3.0	3.2
16	1.3	6-15	18.75	0.19	9.3	72.5	.51	0.67	3.54	1.9	2.1
17	2.0	11-11	22.75	0.28	45.5	38.6	.43	1.75	6.26	4.8	6.6
18	1.2	8	20.75	0.22	29.7	40.9	.47	1.22	5.53	3.9	3.2
19	1.3	8-15	19.5	0.22	18.5	68.3	.52	1.26	5.75	3.9	4.2
20	2.5	13- 9	22.0	0.29	21.5	64.0	.42	1.37	4.73	7.5	3.4
21	2.8	12-15	22.75	0.28	32.6	50.9	.45	1.66	5.91	5.4	3.7
22	3.5	14- 3	23.0	0.31	27.7	51.6	.35	1.94	6.27	9.3	4.1
23	2.0	11-10	22.5	0.27	35.9	43.5	.46	1.86	5.77	5.0	4.0
24	0.1	5-15	18.0	0.18	20.0	53.9	.44	1.08	6.00	3.5	2.6
25	0.2	6- 3	18.0	0.18	10.6	46.4	.46	0.49	2.70	1.4	1.3
26	1.9	12- 3	22.0	0.21	21.5	37.5	.43	0.81	3.86	2.8	1.8
27	1.0	10	22.5	0.26	13.8	42.8	.43	0.50	2.28	2.2	2.2
28	3.2	12-11	23.0	0.29	43.1	31.3	.35	1.35	4.66	5.7	2.4
29	3.4	12- 5	24.0	0.29	25.7	30.2	.42	0.78	2.68	2.9	1.8
30	4.2	14- 5	25.0	0.32	36.2	39.4	.44	1.42	4.45	4.8	3.6
31	0.3	7- 8	20.0	0.21	16.1	20.4	.57	0.82	3.89	2.5	2.4
32	6.8	18- 4	27.5	0.38	51.8	38.3	.39	1.99	5.23	4.1	6.2
33	1.9	11- 3	23.75	0.28	29.8	34.0	.49	1.04	3.70	2.7	2.7
34	0.5	5- 4	17.0	0.16	12.9	42.7	.47	0.55	3.43	2.0	1.6
35	0.5	5- 5	17.5	0.16	17.5	47.7	.37	0.84	5.24	3.4	1.8
36	1.0	9- 7	24.75	0.26	23.1	62.0	.47	1.43	5.50	4.4	3.7
37	0.3	6- 2	17.0	0.17	12.0	61.4	.40	0.74	4.33	3.0	1.9
38	2.2	12- 8	23.0	0.28	33.7	32.6	.45	1.10	3.93	3.5	2.5
39	3.6	12- 8	22.5	0.28	26.7	39.0	.46	1.05	3.74	3.6	2.6
40	1.8	8- 9	20.5	0.23	19.4	41.2	.42	0.80	3.48	3.0	1.8
41	4.6	15- 4	23.5	0.32	23.0	35.4	.40	0.81	2.54	3.2	1.7
42	0.7	7-13	18.75	0.20	15.6	46.4	.50	0.72	3.61	2.1	2.1
43	2.2	7-15	22.0	0.24	23.0	37.0	.39	0.85	3.54	3.3	1.8
44	0.6	8- 5	20.5	0.24	15.4	36.5	.42	0.57	2.36	2.2	1.4
45	5.0	18- 7	25.75	0.37	53.6	29.6	.44	1.59	4.30	4.3	3.5
46	8.9	19-11	27.0	0.39	56.0	24.4	.43	1.37	3.51	6.2	3.6
47	2.0	13- 7	24.0	0.31	28.4	42.3	.43	1.21	3.89	4.1	2.8
48	1.7	9- 5	21.0	0.23	27.2	65.5	.40	1.78	7.75	5.4	4.9

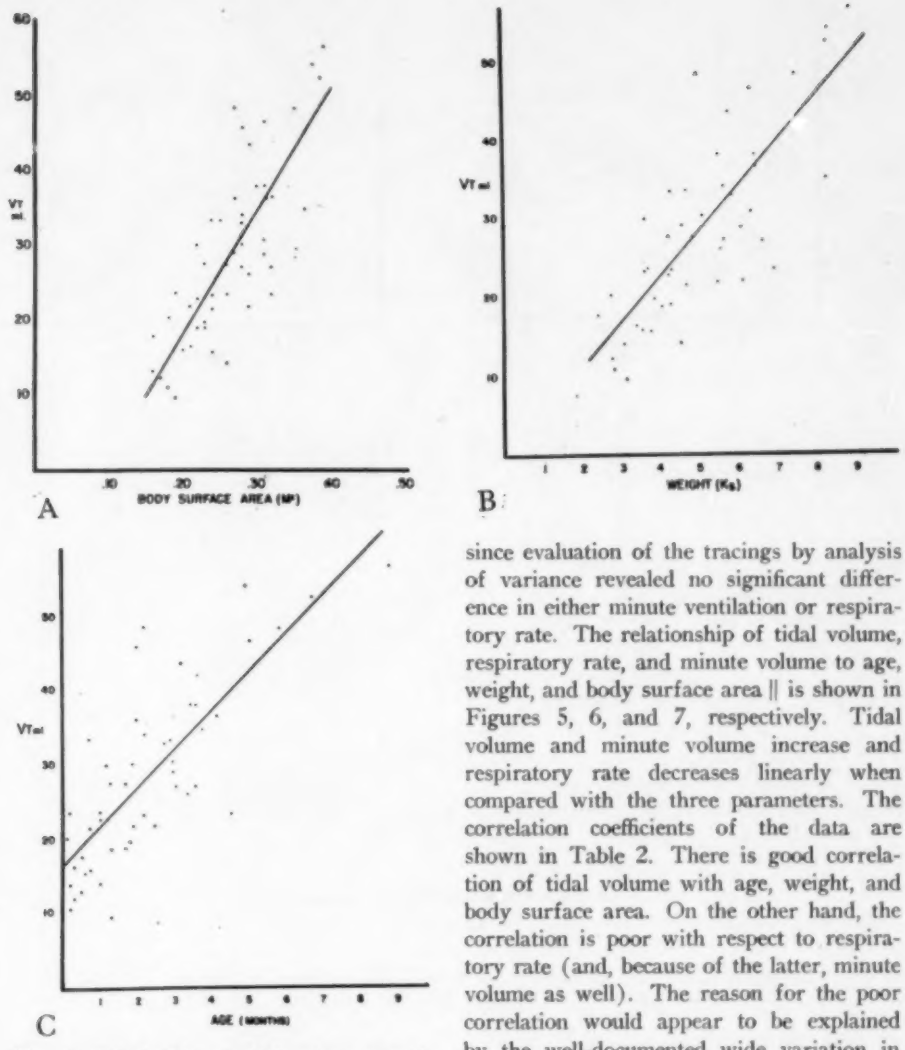

Fig. 5.—Relationship of tidal volume to body surface area (*A*), weight (*B*), and age (*C*). The solid lines represent the regression lines for the data.

Results

The results of the 49 studies are shown in Table 1.§ Where duplicate or triplicate recordings were made on the same patient the means of these observations are shown, since evaluation of the tracings by analysis of variance revealed no significant difference in either minute ventilation or respiratory rate. The relationship of tidal volume, respiratory rate, and minute volume to age, weight, and body surface area ‖ is shown in Figures 5, 6, and 7, respectively. Tidal volume and minute volume increase and respiratory rate decreases linearly when compared with the three parameters. The correlation coefficients of the data are shown in Table 2. There is good correlation of tidal volume with age, weight, and body surface area. On the other hand, the correlation is poor with respect to respiratory rate (and, because of the latter, minute volume as well). The reason for the poor correlation would appear to be explained by the well-documented wide variation in respiratory rate in normal infants.[12]

The average mean inspiratory flow rate was 4.01 L. per minute (range, 1.4-9.3), and that of expiration was 3.15 L. per minute (range, 1.2-7.6). As expected, flow rates increase with size (Fig. 8). The rate of increase is slightly greater with inspiratory flow than expiratory flow. The explanation for this lies in the fact that at

§ All symbols used in the tables and figures are those proposed by a committee of respiratory physiologists.[10]

‖ Body surface area was determined from the nomogram of R. R. Hannon.[11]

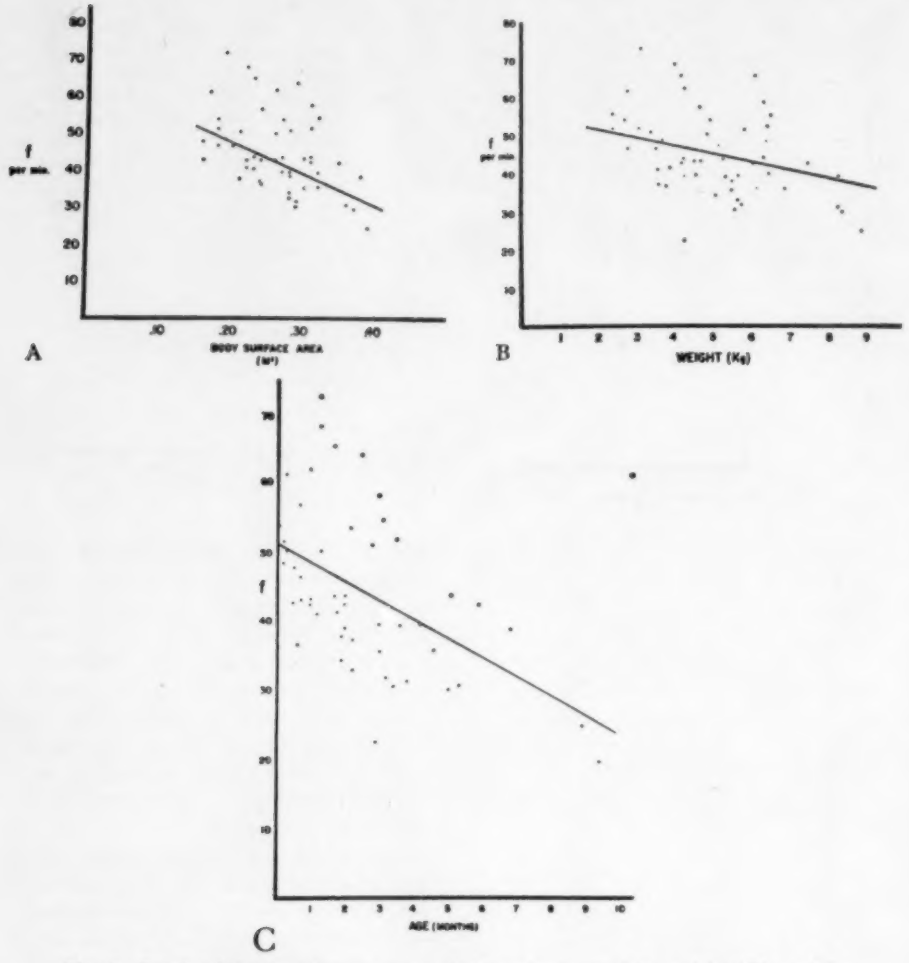

Fig. 6.—Relationship of respiratory rate to body surface area (*A*), weight (*B*), and age (*C*). The solid lines represent the regression lines for the data.

all ages there is essentially no change in the duration of inspiration when compared to the duration of the total cycle, called here the I/T ratio (Fig. 9). In order for this ratio to remain essentially constant as surface area (or age) increases, the inspiratory flow rate must increase slightly more rapidly than expiratory flow.

Comment

Mechanical success when measuring ventilation in infants utilizing a mask-and-bag system depends upon a low dead space and a negligible resistance to the flow of air. With the spirometer used in these studies, the dead space with which one must concern oneself is in the face mask, since the one-way valves prevent rebreathing from the connecting tubes. The measured dead space of the mask was 10 ml. and was certainly less than that when applied because of displacement by the facial structures of some of the dead space. Breathing of increased concentrations of CO_2 in infants, as in

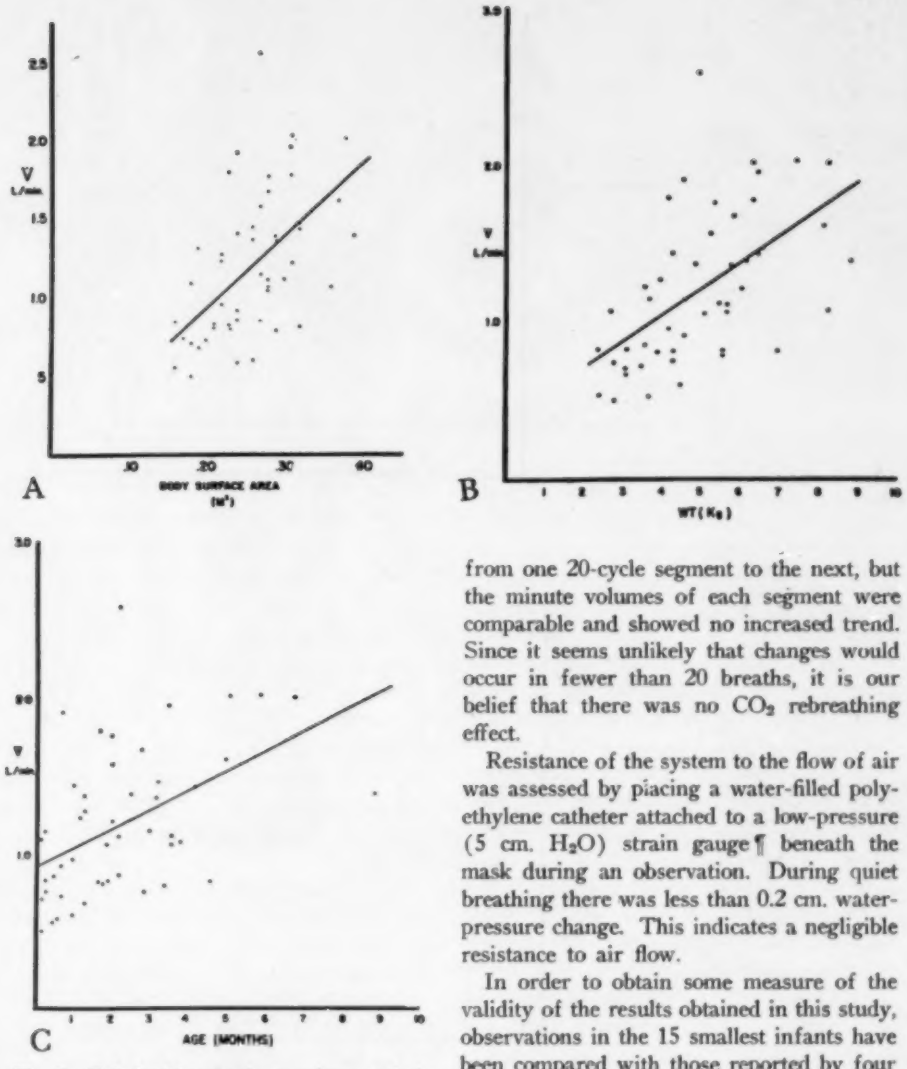

Fig. 7.—Relationship of minute volume to body surface area (*A*), weight (*B*), and age (*C*). The solid lines represent the regression lines for the data.

adults, results in an increase of rate and depth of respiration.[13] Rebreathing was, therefore, investigated by analyzing and comparing the tidal volumes and rates of the first, middle, and last 20 cycles of the records of 30 subjects. Occasionally there was some variation in rate and tidal volume from one 20-cycle segment to the next, but the minute volumes of each segment were comparable and showed no increased trend. Since it seems unlikely that changes would occur in fewer than 20 breaths, it is our belief that there was no CO_2 rebreathing effect.

Resistance of the system to the flow of air was assessed by placing a water-filled polyethylene catheter attached to a low-pressure (5 cm. H_2O) strain gauge¶ beneath the mask during an observation. During quiet breathing there was less than 0.2 cm. water-pressure change. This indicates a negligible resistance to air flow.

In order to obtain some measure of the validity of the results obtained in this study, observations in the 15 smallest infants have been compared with those reported by four

TABLE 2.—*Correlation Coefficients of Tidal Volume, Rate, and Minute Volume Versus Body Surface Area, Weight, and Age*

	Vt	f	Vol.
Body Surface Area, m^2	0.794	−0.427	0.557
Weight, kg.	0.779	−0.306	0.539
Age, Mo.	0.785	−0.466	0.462

¶ Statham Pressure Transducer, Model No. P23D.

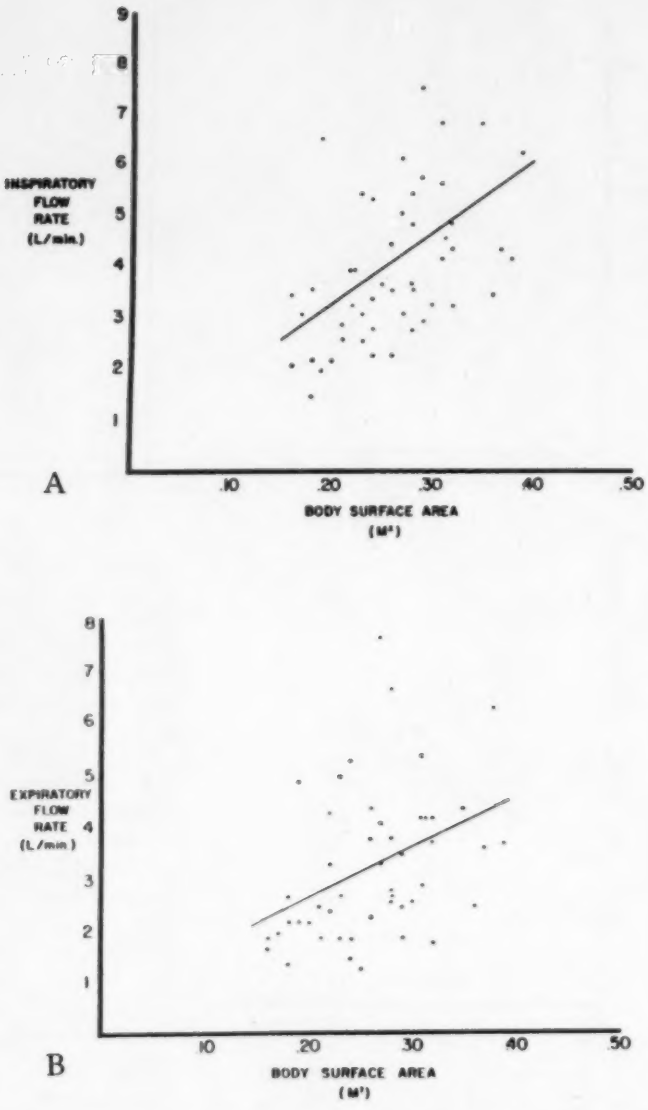

Fig. 8.—Relationship of mean inspiratory and expiratory flow rates to body surface area. *A*, inspiration. *B*, expiration. The solid lines represent the regression lines for the data.

other groups (Table 3). The weights of all subjects were comparable, and all were in a similar state as regards sleeping and time from last meal. The mean tidal volume in the present study compares closely with the observations of Boutourline-Young and Smith, Cross, and Cook. The mean respiratory rate, on the other hand, was considerably greater than all those except Stahlman's. The technique employed by Stahlman and ourselves was similar, while the others compared here used the plethysmographic method. It would seem improbable that the differences in methodology would account for the discrepancies in rate, as suggested by Stahlman, i. e., that the mask-and-bag system is more sensitive and would record respirations missed by the

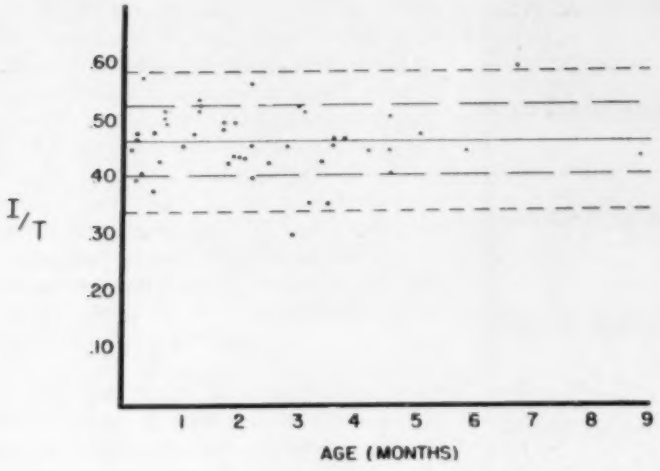

Fig. 9.—Relationship of the inspiratory-total cycle time ratio to age. There is little change in the ratio (0.47) with age. The solid line represents the regression line of the data, and the broken lines represent 1 and 2 standard deviations from the mean.

plethysmographic method. Except in the very young infant, small irregular excursions which might be missed by the indirect method were not observed. On the contrary, our observations would emphasize the remarkable rhythmicity of respiration (Fig. 10), a feature also noted by Kaye, Whittenberger, and Silverman.[14] It appears unlikely that the differences could be due to variations in room temperature (73-85 F in this study) or to difference in the steady state. The observed differences are most likely attributable to the wide range of normal rate previously alluded to. In addition to group variation, there may well be day-to-day variation in the same subject. This is suggested by the observations on Case 8, who, on two successive days, when sound asleep, had a rate increase of 42.9 to 56.9 and tidal volume from 21.2 to 33.3 ml.

Minute ventilation was much higher in the present study and in that of Deming and Washburn. This is most likely a function of age, although Washburn has recently suggested that altitude may have played a role in the increased minute ventilation in his series.[15] His studies were performed in Denver, the others shown in Table 3 were performed at or near sea level.

There should be a high correlation between size (weight or body surface area) and alveolar ventilation in infants while in a steady state,[8] even though minute ventilation shows considerable variation owing to the wide range in respiratory rate. Respiratory dead space was not measured in this study. However, if one assumes the

TABLE 3.—*Comparison of Ventilatory Data of Present Study with That of Other Investigations Among Infants of Comparable Weights*

Investigator	No.	Range	Weight, Kg.	Vt, Ml.	f	Vol., L.
Deming-Washburn	27	1 day-3.2 mo.	——— (2.5-5.3)	27.3	41	1.07
Cross	36	12 hr.-13 days	3.48 (2.53-5.0)	17.5	28.6	0.59
Boutourline-Young	17	4 hr.-72 hr.	3.53	16.8	39	0.64
Cook et al.	25	5 hr.-7 days	2.90 (2.42-4.08)	15.6	33.3	0.52
Stahlman	44	9 hr.-4 days	3.25 (1.81-4.09)	9.2	52.2	0.48
Oliver et al.	15	3 days-2.2 mo.	3.23 (2.4-4.0)	17.1	30.8	0.53

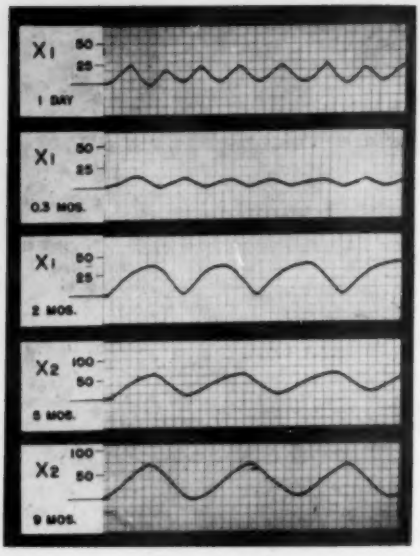

Fig. 10.—Respiratory tracings in infants of varying ages. Age and calibration is shown at the left of each trace. To be noted is the rhythmicity of respiration.

dead space on the basis suggested by Radford, Ferris, and Kriete,[16] i. e., that respiratory dead space in milliliters is equal to body weight in pounds, alveolar ventilation can be calculated. When this is done a poorer correlation coefficient (0.411 and 0.377 for body surface area and weight, respectively) is found than with minute volume (Table 2). The assumption made by Radford is not supported by these data, and it is further concluded that the nomogram described by him for prediction of tidal volume in subjects with restrictive ventilatory insufficiency should not be used for infants. It cannot be stated from our observations at what size the assumption becomes sufficiently accurate to permit use of the nomogram. The smallest subject in whom dead space was measured by Radford weighed 57 lb.

The relationship between minute ventilation in small infants and in older children and adults was investigated. Twenty-four

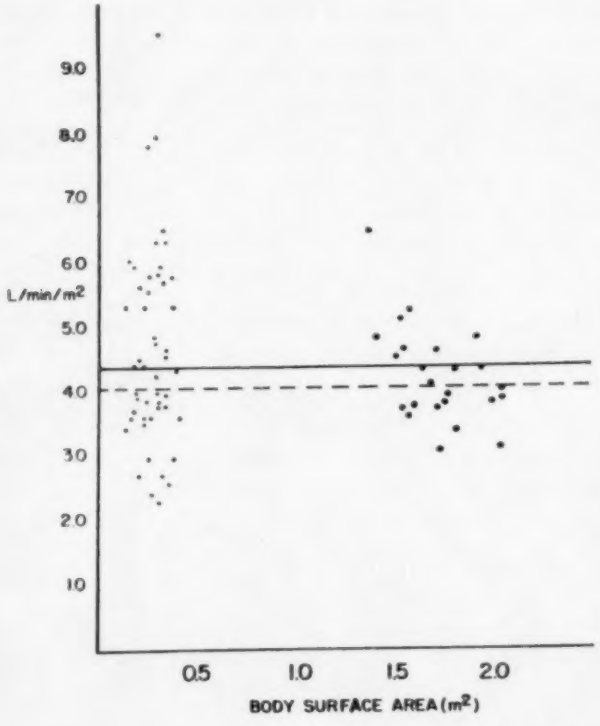

Fig. 11.—Comparison of minute ventilation and body surface area in infants with older children and adults. The solid line indicates the median for the infants, the broken line the median for the adults. A close correlation of the two groups of data is apparent.

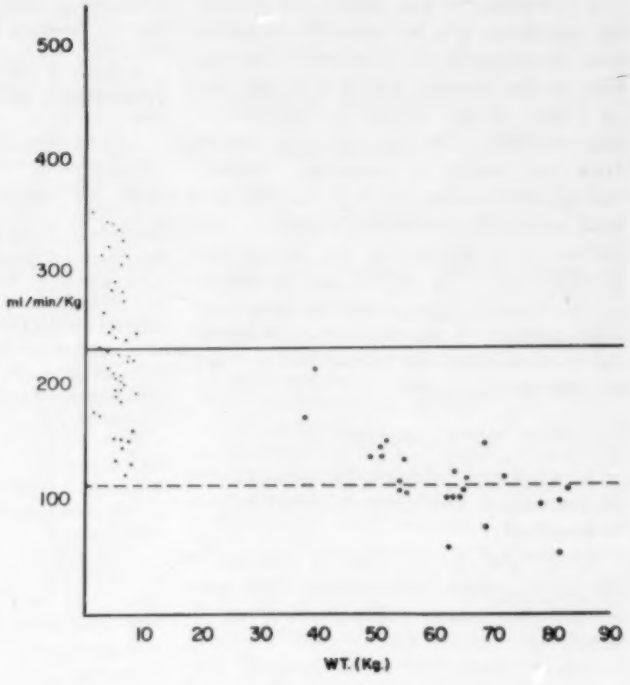

Fig. 12. — Comparison of minute ventilation and body weight in infants and older children and adults. The solid line indicates the median for the infants, the broken line the median for the adults. Lack of correlation of these two groups is apparent.

subjects ranging in age from 14 to 33 years had measurements of minute ventilation made with use of a 9 liter spirometer.# In an attempt to make these subjects comparable to the infants all 24 were measured 30 to 90 minutes postprandial, after at least 20 minutes of rest, and were presumed to be in a steady state.[17] Ventilation when corrected to unit of body surface area in infants and adults is very comparable (Fig. 11). Because there has recently arisen criticism of the use of body surface area rather than weight as a measurement in comparing ventilation and metabolism,[18,19] the data are also plotted versus weight (Fig. 12). As can be seen, no adult value lies above the median for infants, nor does any infant value lie below the median for adults. It is concluded from these observations that body surface area serves as a better measurement than weight for comparing minute ventilation in persons of widely varying size.

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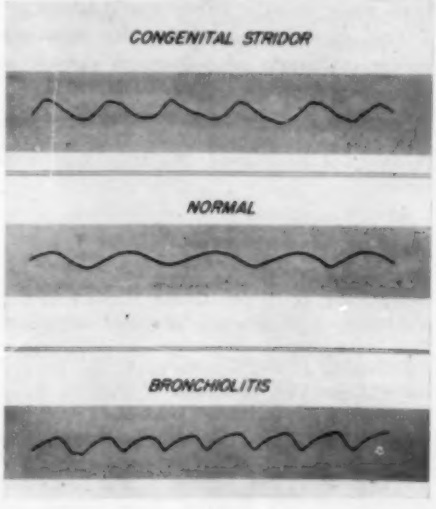
Fig. 13.—Abnormal breathing patterns in infants. Upper tracing: laryngeal stridor. Note the prolonged, irregular inspiratory pattern. Middle tracing: normal infant. Lower tracing: bronchiolitis. Note the initial, brief, rapid expiratory flow followed by a prolonged, slow, expiratory flow.



It is hoped that this method for measuring ventilation will be applicable to infants with disturbances of ventilation. Preliminary studies indicate such will be the case. In Figure 13 are shown two examples of abnormalities. The alterations in pattern from the normal is apparent. Pneumotachographic studies on a 5-year-old child with asthma [14] revealed an expiratory flow pattern very similar to the infant with bronchiolitis. The effect of therapeutic agents measured by spirometry before and after therapy is an obvious extension of the method described herein and is being carried out at present.

Summary

A spirometer adapted for measurement of pulmonary ventilation in small infants is described.

Forty-eight normal infants ranging in age from 3 days to 8.9 months have been studied, and their values are given in detail.

Linear correlation exists between age, weight, and body surface area and tidal volume, minute ventilation, and respiratory rate.

Observed values of minute ventilation in these infants when compared with body surface area correlate well with observations made in older children and adults.

The possibility of utilizing this technique in the evaluation of pulmonary disease in infancy is suggested.

Statistical assistance was provided by W. B. McIntosh, Assistant Professor, Department of Zoology and Entomology, The Ohio State University.

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Protein Studies in Normal Newborn Infants

Paper Electrophoresis of Cerebrospinal Fluid and Serum

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Serum protein fractions have been studied intensively in the normal newborn infant.[1-9] However, there is only sparse information on the cerebrospinal fluid protein fractions in this age group.[10-18] The concentration of the low protein content in small amounts of cerebrospinal fluid has presented a major problem. Earlier studies primarily used precipitation methods which could not separate the individual fractions. The use of dialysis methods for concentrating proteins, combined with paper electrophoresis, now affords adequate means for separation of the various components of cerebrospinal fluid proteins.

Paper electrophoretic studies of cerebrospinal fluid have been performed for the most part only in adults and older children,[19-22] with few reports in normal newborn infants.[17,18] The purpose of this study was to determine the distribution and relationship of proteins in the cerebrospinal fluid and serum of normal newborn infants utilizing chemical and paper electrophoretic methods.

Method

Thirty-five normal newborn infants ranging in age from 2½ hours to 114 hours were studied. All were products of full-term uneventful gestation and deliveries and on subsequent observations for at least two months were apparently normal.

Submitted for publication Oct. 15, 1958.

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Paper read by title at the 68th Annual Meeting of the American Pediatric Society, Atlantic City, N. J., May 8-9, 1958.

This study was supported in part by Grant RG4032 (C3) U. S. P. H. S., a fellowship from National Infantile Paralysis Foundation, and a grant from the Association for the Aid of Crippled Children.

Approximately 3 ml. of cerebrospinal fluid were obtained by lumbar puncture, centrifuged immediately to remove any erythrocytes, and kept in a frozen state until processed. Blood samples were obtained by femoral venipuncture, allowed to clot for approximately one hour, and centrifuged, and serum was removed for analysis.

The concentration of total protein in the serum and cerebrospinal fluid was determined by a modification of the Biuret method.[23] In preparation for paper electrophoresis, 2 to 3 ml. portions of cerebrospinal fluid were concentrated in an Oxford Model B dialyzer for three hours against a 30% solution of polyvinyl pyrolidone (P. V. P.). Eight strips of Whatman 3 MM filter paper were run simultaneously. Barbital (Veronal) buffer at pH 8.6 and 0.05 ionic strength was used. After initial equilibration, serum or cerebrospinal fluid was applied at the apex of the wet strip, 10 microliter portions of serum and 100 microliter portions of the cerebrospinal fluid concentrate were applied in duplicate. A constant current of 6-9 ma. was employed for 16-hour runs. After drying at 90-120 C for 30 minutes, strips were stained with amidoschwarz 10B dye solution for the protein distribution pattern. Densitometry was performed with a Spinco Servo-Type integrating scanner. In this type of scanner, the area under the density curves is shown by a corresponding series of pips. For each component, the Gaussian distribution curve was approximated and lines were drawn through the intersections of the curves for adjacent components.

Results

The cerebrospinal fluid proteins occurred in the electrophoretic patterns as five bands, depicited in Figure 2 with their corresponding paper strip, in the order of increasing mobility to γ-, β-, α_2-, and α_1-globulins and to albumin. In addition to these protein components, cerebrospinal fluid contains a prealbumin or X-fraction which moves faster than the albumin component. A comparison with the serum protein distribution pattern (Fig. 1) reveals that the components

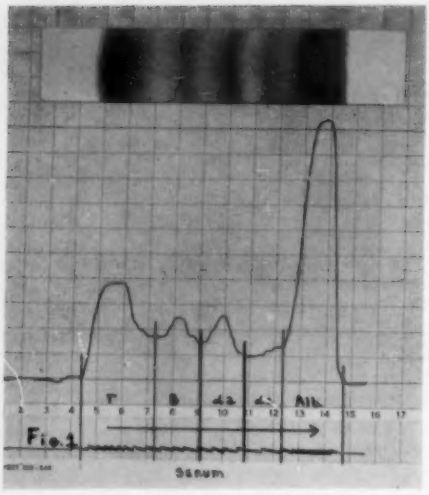

Fig. 1.—Amidoschwarz 10B-stained electrophoretic serum pattern with integrated densitometry curves. Typical serum protein pattern of normal newborn infant.

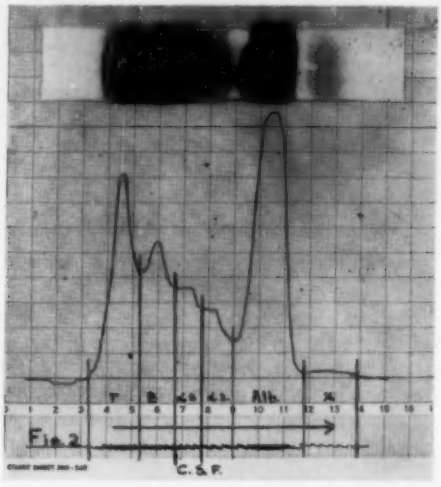

Fig. 2.—Amidoschwarz 10B-stained electrophoretic cerebrospinal fluid pattern with integrated densitometry curves. Typical cerebrospinal fluid pattern of normal newborn infant.

and rates of mobility of cerebrospinal fluid protein and those of serum are essentially the same except for the addition of the X-fraction in cerebrospinal fluid (Figs. 1 and 2).

The range of values with means and standard errors obtained for the cerebrospinal fluid and serum proteins in this series are presented in Table 1. The amount of total protein found in the cerebrospinal fluid (0.07 ± 0.006 gm. %) is relatively small in comparison to serum values (5.7 ± 0.19 gm. %). A comparison of the various components of the cerebrospinal fluid and serum proteins shows that they are essentially the same, except for the addition of the X-fraction in cerebrospinal fluid ($2.5 \pm 0.33\%$) and a significant decrease in the albumin fraction of cerebrospinal fluid ($P = <0.02$). The albumin percentage of cerebrospinal fluid is 47.4 ± 1.24 as compared with serum values of $52.1 \pm 1.47\%$. However, if one combined the percentage of the prealbumin (X-) fraction (2.5 ± 0.33) in the cerebrospinal fluid with that of the albumin fraction (47.4 ± 1.24), there would be no apparent significant decrease in the albumin fraction of cerebrospinal fluid as compared to serum (52.1 ± 1.47). The decrease in the A/G ratio of cerebrospinal fluid (0.90 ± 0.06) compared to serum (1.09 ± 0.12) is not statistically significant.

TABLE 1.—*Protein Percentage of Thirty-Five Clinically Normal Newborns* *

		Total Protein, Gm. %	A/G Ratio	Prealbumin, %	Albumin, %	Globulin			
						α_1, %	α_2, %	β, %	γ, %
CSF	Range	0.027-0.090	0.74-1.67	0-5	42.6-62.5	1.8-10.6	3.3-15.5	6.6-27.3	15.8-29.4
	Mean	0.07	0.90	2.5	47.4	6.8	8.8	14.5	20.0
	Standard error	±0.006	±0.06	±0.33	±1.24	±0.42	±1.30	±1.10	±1.41
Serum	Range	4.93-6.97	0.77-2.28		43.3-69.5	1.6-7.4	3.3-12.5	9.2-26.7	14.1-24.0
	Mean	5.71	1.09		52.1	5.0	8.0	14.9	20.0
	Standard error	±0.190	±0.12		±1.47	±0.27	±0.11	±0.70	±0.70

* Obtained from amidoschwarz 10B-stained cerebrospinal fluid and serum patterns prepared in hanging-strip paper electrophoresis.

A comparison of the rest of the protein pattern percentages shows essentially similar results in the cerebrospinal fluid and serum. In the cerebrospinal fluid, the mean percentage of α_1 was 6.8; α_2, 8.8; β, 14.5, and γ, 20; whereas in the serum, α_1 was 5.0; α_2, 8.0; β, 14.9, and γ, 20.

Comment

The present investigation was made in order to establish protein values in normal newborn infants, since most of the reported studies employing cerebrospinal fluid electrophoretic techniques have concerned adults, older children, and abnormal infants of varying ages.[10,19-22]

The concentration of cerebrospinal fluid with its low protein content has presented many difficulties, since the paper-electrophoretic separation of the various protein components requires a 2%-5% protein solution. This necessitates a concentration of cerebrospinal fluid depending upon the initial total protein content. In adults the protein concentration in cerebrospinal fluid is approximately $\frac{1}{300}$ that of serum. In our series of newborns this ratio is approximately 1:80. Even though the protein concentration in cerebrospinal fluid is higher in the newborns, the limited amount obtainable in infants as compared to adults requires a special technique for concentrating to the desired strength so that electrophoretic patterns may be secured. In the present investigation it was possible to obtain the necessary concentration utilizing only 2-3 ml. aliquots of cerebrospinal fluid, employing essentially the dialyzing technique of Grogan and Roboz.[24]

TABLE 2.—*Earlier Investigations of Total Protein in Cerebrospinal Fluid of Normal Infants During the First Fourteen Days of Life with Use of Various Precipitation Methods*

Author	Cases, No.	Range of Protein Values, Mg/100 Ml.	Mean
Waltz (1928)	22	30-100	--
Samson (1931)	32	40-80	60
Ujsaghy (1936)	--	--	45
Spiegel-Adolph (1954)	14	--	103.35
Wyers & Bakker (1954)	50	33-162	96

The variation in methodology makes it difficult to evaluate the results of various authors even in older children and adults. In general, cerebrospinal fluid protein values of 15-30 mg/100 ml., with an upper limit of 45 mg/100 ml., are accepted as normal in children beyond infancy.

The lack of controlled data concerning the patterns of cerebrospinal fluid in the newborn infant makes a comparison of the results in this study (Table 1) with the findings of previous investigators (Tables 2 and 3) difficult. For instance, a comparison with the report by Widell [17] shows that cerebrospinal fluid total protein and albumin values by this author are higher than those found in our study and that lower α_1-, α_2-, β-, and γ-globulin levels are noted. A study by Otila,[16] with use of a colorimetric method, has shown total cerebrospinal fluid protein values in small prematures of more

TABLE 3.—*Cerebrospinal Fluid Electrophoretic Patterns as Reported by Other Investigators in Infants and Normal Adults*

Author	No. Cases (Age)	Total Protein, Mg/100 Ml.	Prealbumin, %	Albumin, %	Globulin					A/G
					α_1, %	α_2, %	β_1, %	β_2, %	γ, %	
Widell (1958)	10 (1st wk. of life)	80.9	1.2	76.7	2.4	3.6	5.7	2.9	6.5	--
Koch (1956)	3 (1st wk. of life)	64	--	43.1	9.1		16.9		30.9	0.8
		64	2.1	56.1	4.3	6.9	14.9		15.7	1.3
		16	1.8	50.8	6.7	8.9	17.7		14.3	1.1
Wagenhöfer (1954)	10 (adult)	--	7.2	52.3	12.3		18.8		9.51	--
Plückthun (1953)	10 (adult)	--	4.4	52.4	5.3	8.1	18.3		11.5	--
Schneider et al. (1951)	5 (adult)	--	--	56.5	9.8		15.8		18.8	--

than 100 mg/100 ml. in the first month of life decreasing to 50-75 mg/100 ml. in the second to third month. However, serum values in our investigation are similar to those reported in full-term infants by Saito et al.[9]

In the present investigation, the mean for the total protein value of cerebrospinal fluid in normal full-term newborn infants was found to be 70 mg/100 ml., which is higher than that reported by others in adults [19-22] but less than that reported in premature infants.[16] A comparison of cerebrospinal fluid results in our series of newborn infants with those in adults shows a lower A/G ratio as a result of the decrease in albumin fraction in the newborn (Table 1). The distribution of albumin and globulin in normal cerebrospinal fluid indicates a similarity to that of serum, except for a decrease in albumin percentage and the presence of a small amount of the prealbumin or X-fraction found only in cerebrospinal fluid. This X-fraction was first described by Kabat and his group [25] in 1942, and its chemical properties have been reported by Aly [26] and Wagenhöfer and Zucha.[21] This fraction migrates faster than albumin and is usually not demonstrated on fractionation of serum. Its exact significance has not been determined. In the present series of newborns the mean percentage for this fraction was 2.5 ± 0.33.

The variations in normal cerebrospinal fluid total protein values for the different age groups (highest in the premature, decreasing in the normal full-term infant, and lowest in the adult) suggest that immaturity of the blood-cerebrospinal fluid barrier and, therefore, increased permeability of this barrier is likely to be a factor in the changes seen in total protein content. On this basis, it would be expected that the premature infant should show the highest cerebrospinal fluid protein content. An accurate comparison of the various protein components of the cerebrospinal fluid of varying age groups is not possible at this time because of the limited data.

The results obtained in our study of normal newborn infants may, therefore, serve as a basis for comparison in further studies on factors influencing the cerebrospinal fluid and serum proteins in infants with abnormal conditions. Cerebrospinal fluid and serum levels are now being studied in newborns with suspected intracranial pathology and those with a history of complicated gestation or abnormal delivery. In this way, the changes which the components of proteins undergo during disease processes may possibly be used as an aid in diagnosis and as an index of successful therapy.

Summary

Cerebrospinal fluid and serum protein values were evaluated by paper electrophoresis in 35 full-term normal newborn infants ranging in age from 2½ to 114 hours. Cerebrospinal fluid and serum total protein values were also determined.

The total protein concentration of cerebrospinal fluid in this group ranged from 25 to 90 mg/100 ml. (mean, 70 ± 6 mg/100 ml.) which is significantly higher than the normal values reported for older children and adults (15-30 mg/100 ml.).

Comparison of the protein components of cerebrospinal fluid and serum shows a prealbumin (X-) fraction in cerebrospinal fluid ($2.5 \pm 0.33\%$) which is not present in serum and a significant decrease in the albumin fraction of cerebrospinal fluid (albumin percentage of 47.4 ± 1.24 in cerebrospinal fluid as compared to 52.1 ± 1.47 in serum, $P = <0.02$). If the percentages of prealbumin (X-) are combined with the albumin fraction, there would be no apparently significant difference between cerebrospinal fluid and serum values. The following percentages (mean and standard error) were found for the protein components of the cerebrospinal fluid in this series: $\alpha_1 = 6.8 \pm 0.42$; $\alpha_2 = 8.8 \pm 1.30$; $\beta = 14.5 \pm 1.10$, and $\gamma = 20 \pm 1.41$. A comparison of results obtained on fractionation of the components in the cerebrospinal fluid with those in older children and adults shows a decrease in the albumin fraction.

Dr. R. E. Hosbach, Mr. R. P. Altman, Mrs. C. Mahairas, Miss J. Mestern, and Mrs. C. Piliero gave technical assistance during the course of this investigation.

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Trimethadione (Tridione) Nephrosis

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Trimethadione (Tridione) was first shown to be highly specific in petit mal epilepsy by Perlstein in 1946, and this has been amply confirmed by Lennox and others.[1] It was recognized early that toxic side-effects may follow prolonged administration of the drug, such as dermatitis, hepatitis, photophobia, drowsiness, nausea, aplastic anemia, and agranulocytosis. Barnett and co-workers[2] reported the first case of nephrotic syndrome following the use of trimethadione in 1948. Since then, four more cases have been reported with one death.[3-5,7] One case followed the use of paramethadione (Paradione),[6] a related drug. We are adding two additional cases of nephrosis following the trimethadione treatment for petit mal, both of which ended fatally.

Report of Cases

CASE 1.—This was the first Maimonides Hospital admission of a 6-year-old white boy, who entered the hospital in coma on May 12, 1951. Four days prior to his admission the mother first noticed some swelling of the eyelids. After 48 hours this swelling disappeared. On the following morning edema was again evident, this time involving the entire face and the extremities. On the next morning, the fourth day of illness, the child appeared to be in coma. A urine examination at this time revealed a 4+ albuminuria. A diagnosis of nephrosis was made, and the child was admitted promptly to the hospital.

Past History.—The patient was born at full term and had a spontaneous delivery. At about the third to fourth month of life, some suspicion was aroused that development was not proceeding normally. At about 11 months of age, the first convulsion occurred. A diagnosis of cerebral palsy with mental deficiency was made at that time. Convulsions at first were generalized, but after several months they became milder and resembled petit mal, occurring several times a day and consisting of stiffening of the body with momentary loss of consciousness. At 4 years of age trimethadione was started. Blood counts were done regularly every month throughout the period of observation. About six months before admission, urine examination was performed and found to be normal.

Family History.—Both parents were alive and well. There was no history of familial or hereditary diseases.

Physical Examination.—Examination revealed a well-nourished, well-developed child in coma. Temperature, pulse, and respirations were normal. Blood pressure was 135/86 mm. Hg. The face, especially around the lids, was moderately edematous. There was no abnormality of the ears, nose, and throat. The lungs were clear to percussion and auscultation. The heart was not enlarged to percussion. The point of maximal impulse was not seen or felt. There was a regular sinus rhythm, and no murmurs were heard. The abdomen revealed no evidence of ascites. The liver and spleen were not palpable, and no masses were felt. There was moderate spasticity of all extremities, especially marked on the left side. The left knee jerk was more active than the right. Babinski and ankle clonus signs were not elicited. Moderate edema was present in all extremities, the abdominal wall, and the scrotum.

Laboratory Findings.—Urinalysis revealed 4+ albuminuria with many hyaline and granular casts. There was an occasional red cell in the urine. Glucose and acetone tests were negative. The specific gravity ranged from 1.010 to 1.040. The blood count showed 6,600,000 red blood cells and 36,000 white blood cells per cubic millimeter. The differential count showed 56% segmented forms, 38% lymphocytes, and 6% monocytes. The corrected sedimentation rate of the erythrocytes was 21 mm. in one hour. Blood chemistry studies revealed urea nitrogen 22 mg. per 100 cc., and on subsequent examinations revealed a steady rise to 34, 50, and 58 mg. per 100 cc. Serum cholesterol concentrations were 645, 488, 755, and 666 mg. per 100 cc. on consecutive drawings. The total protein was 3.9 gm. per 100 cc., of which 0.9 gm. was albumin and 3.0 gm. globulin. Subsequent examinations showed total protein concentrations of 3.6 and 3.7 gm. per 100 cc., with 1.3 and 1.0 gm. of albumin, and 2.3 and 2.7 gm. of globulin. Blood cultures on two occasions revealed no growth. The

Submitted for publication Nov. 6, 1958.

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weight of the patient in the hospital on admission was 45 lb., 6 oz., and there was a steady rise to 51 lb., 12 oz. before death. The blood pressure on admission was 135/86; on the second hospital day it was 124/82, and two days before death it was 132/100.

Course in the Hospital.—Trimethadione was suspected as a cause of the nephrosis at the very onset of the present illness and was promptly discontinued. Intravenous fluid, 5% dextrose in water, was begun immediately after admission. Within 24 hours, the child began to improve. By the end of the second hospital day, he was well oriented. However, his weight continued to increase steadily in spite of treatment. On the 13th hospital day, in view of the relentless course of the disease, it was decided to try corticotropin (ACTH). He received 15 mg. of corticotropin every six hours for four days. On the 16th hospital day, the patient suddenly lapsed into coma with complete circulatory collapse and died within 30 minutes. A postmortem examination was not obtained.

CASE 2.—This was the first Maimonides Hospital admission of a 9-year-old white girl, who entered with a chief complaint of puffiness of the face.

Family History.—Both parents were alive and well. There was no history of familial, hereditary, or nervous diseases in either family.

Present Illness.—At 6 years of age, three years prior to admission, the mother noticed that the child dropped her head on occasions, or made some other curious movement for very short periods. The parents paid no special attention to these seizures and did not seek medical aid until six months prior to admission. At this time, the seizures were more frequent, the trances often lasting for 10 seconds. She never had grand mal seizures. A diagnosis of petit mal was made, and trimethadione, 0.15 gm. three times daily, was prescribed. On trimethadione therapy, the number of seizures was gradually reduced, and there were no seizures for the month prior to admission. Blood counts were performed every three to four weeks while she was receiving the medication. About two weeks prior to admission, she had a "head cold." Shortly thereafter, her face and legs appeared to be puffy, and she complained of feeling tired. Four days later, she appeared pale and vomited several times. Her temperature was within normal range. An allergic reaction was suspected. Trimethadione was discontinued, and an antihistamine was prescribed. About five days before admission, the abdomen was noted to be distended. At this time, an examination of the urine revealed a 4+ albuminuria. A diagnosis of nephrosis was made, and hospitalization was advised.

Past History.—Past history revealed a normal birth, feeding, and development pattern with the usual childhood illnesses. Four and one-half years prior to admission, she fell from a sliding pond and was unconscious for five minutes. She was kept in bed for two weeks and made an uneventful recovery.

Physical Examination.—Examination revealed a pale, 9-year-old white girl, appearing chronically ill. There was edema of the face, scalp, and eyelids. The pupils reacted to light, and the fundi were within normal limits. The ears were normal. The child had no difficulty opening her mouth, and the mucous membranes were clear. There was no hyperplasia of the gums. The tongue was moist and clear. The pharynx appeared normal. There were a few nontender posterior cervical nodes in the neck. A few small shotty nodes were felt in the left axilla and in both inguinal regions. The chest expanded equally on both sides and revealed decreased to absent vocal fremitus below the fourth intercostal space posteriorly and bilaterally. There was dullness to percussion, and also diminished breath sounds in the area described. No râles were heard. The heart was not enlarged to percussion. The point of maximal impulse was not seen or felt. There was a regular sinus rhythm with a rate of 108 beats per minute. The heart sounds were distant and muffled. No murmurs were heard. The abdomen was distended, and the skin was edematous. A fluid wave with shifting dullness was elicited. The spleen, liver, and kidneys were not felt. There was slight presacral edema. Moderate pretibial and ankle edema were present. No cyanosis or clubbing of the extremities was noted. The genitals were normal. Neurological examination revealed diminished deep tendon reflexes. Abdominal reflexes were present. No abnormal reflexes were elicited.

Laboratory Findings.—Urinalysis revealed 4+ albuminuria, few to many white blood cells, with occasional clumps and an occasional red blood cell. There were numerous hyaline and granular casts. Glucose and acetone tests were negative. Specific gravity varied from 1.014 to 1.027.

The blood count showed 5,000,000 red cells and 12,500 white cells per cubic milliliter. The hemoglobin content was 15 gm. per 100 ml. The differential count showed 66% segmented forms, 8% band forms, 20% lymphocytes, and 6% monocytes. The corrected sedimentation rate of the erythrocytes was 32 mm. in one hour. The stool examination for blood, ova, and parasites was negative. Blood chemistry studies revealed a glucose concentration of 92 mg. and a urea nitrogen of 11 mg. per 100 cc. The total protein was 3.7 gm. per 100 cc., of which 0.8 gm. was albumin and 2.9 gm. globulin. A repeat examination revealed a total protein content of 4.1 gm. per 100 cc., of which 0.7 gm. was albumin and 3.4 gm. was globulin. The carbon dioxide content was 29.2 mEq. per liter, chlorides 100 mEq. per liter and potassium 7.0

mEq. per liter. Total serum cholesterol concentration was 586 mg. per 100 cc., of which 386 mg. was esters. A repeat examination revealed a total cholesterol content of 816 mg. per 100 cc. of serum. Nose and throat cultures revealed Staphylococcus albus, Neisseria (Micrococcus) catarrhalis and nonhemolytic Streptococcus. Total lipid content was 2.17 gm. per 100 cc.

The electroencephalogram revealed spike activity focal to the right occipital region with spread to the left occipital and the right temporoparietal regions.

Roentgenogram report of the chest revealed congestion and stasis in the basal portions of both lungs. Study of the abdomen revealed edema of the soft-tissue structures as well as ascites.

Course in the Hospital.—The patient was in the hospital for 10 days. On admission, she was given oral penicillin, 200,000 units twice a day. There was no apparent change in her condition for the first eight days. On the ninth hospital day, an area of edema and redness, involving the vulva and extending over the left inguinal region and thigh, was noted. There was a slight elevation in temperature. The diagnosis was erysipelas. The patient was given penicillin, 300,000 units twice a day, intramuscularly. The next morning it was noted that the area of redness had extended up to the left chest, almost into the left axilla and across the midline to the right abdominal wall. She was restless and complained of pain over the erythematous area. The penicillin dosage was increased, and sulfadiazine and tetracycline were added. Barbiturates and codeine were given for sedation. Over the next few hours, she became critically ill. The lesion spread over the entire chest and thighs. She developed a marked pallor, grunting respiration, and a distended abdomen. She was placed in an oxygen tent; a blood transfusion was given, and chloramphenicol (Chloromycetin) and cortisone were added. The patient's condition continued to deteriorate, and the blood pressure was unobtainable. Despite the use of levarterenol bitartrate (Levophed) and corticotropin intravenously, the respirations became very shallow; the temperature rose to 105.6 F, and the patient died, about 36 hours after the onset of the erysipelas.

A partial postmortem examination was permitted. A microscopic anatomical report is herewith given, as interpreted by Dr. Abraham Kantrowitz, Pathologist of Maimonides Hospital.

Heart.—The endocardium and pericardium are normal. The myocardium is free of cell infiltration or exudate. The individual fibers reveal neither cytoplasm nor nuclear abnormalities. The vessels are intact.

Liver.—The capsule is normal. The parenchyma reveals normal lobular architecture. The sinusoids of the central and middle zones are dilated with red blood cells. The central veins are dilated, as well. The portal triads are free from abnormalities. The liver cells are unremarkable.

Kidney.—The surface is thin and smooth. The glomeruli are normal in size and distribution. The glomerular tufts are fused to each other to a moderate degree. Adhesions to Bowman's capsule are found in areas. The basement membranes are thickened and moderately hyperchromatic, with basophilic tendency (Fig. 1.) Infrequent wire loopings to graded degrees of thickening of the basement membranes are noted (Fig. 2). The glomeruli contain a normal amount of blood. Bowman's capsule is thin. The tubules reveal extensive vacuolization of cytoplasm. The vessels are filled with red blood cells. The vascular walls are intact. Lymphocytic infiltrations are found around the

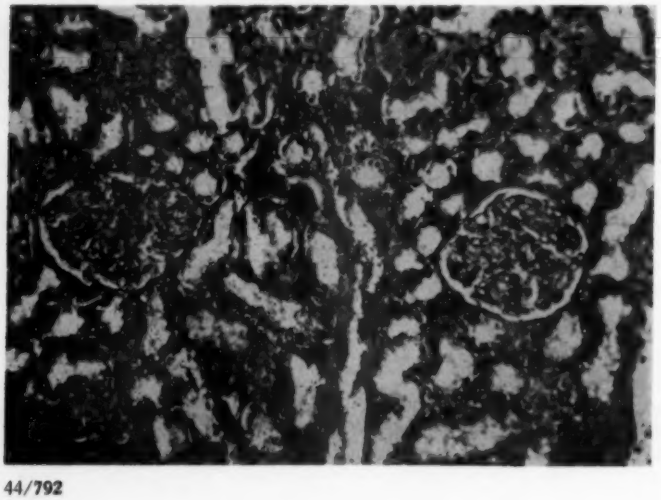

Fig. 1 (Case 2).—Thickening and splitting of basement membrane, adhesions and distortions of the glomerular tufts.

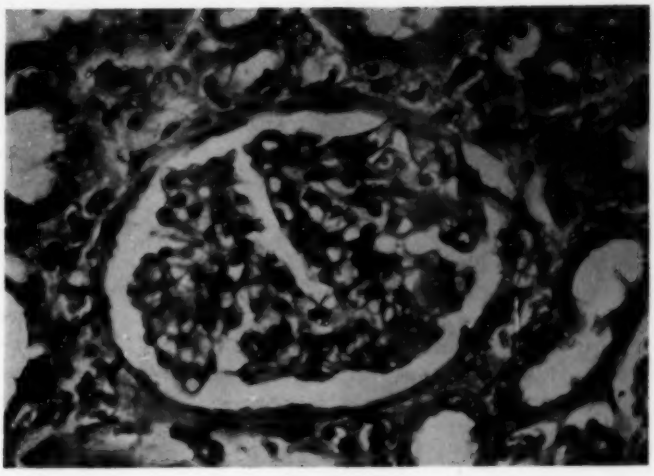

Fig. 2 (Case 2).—Wire looping and thickened basement membrane.

veins and in the venous walls. Scattered small foci of lymphocytic infiltration are also present in the parenchyma. In periodic acid-Schiff staining, the thickened basal membranes are stained bluish-violet. The convoluted tubules and cortical portions of Henle's loop contain numerous slightly sudanophilic and birefringent globules.

Diagnosis.—Membranous glomerulonephritis with nephrotic component. Passive congestion of liver.

Comment

Both cases presented were obvious cases of nephrotic syndrome. After 24 and 6 months of trimethadione treatment for petit mal attacks with good results, the children developed generalized edema and all the other signs of neprhosis.

The interesting part of the first case was the early onset and recurrence of coma. This is a very rare occurrence in lipid nephrosis. The patient responded rapidly to intravenous therapy, and for a period of 16 days he appeared well oriented. However, during this time, the urea concentration in his serum was rising steadily from 22 to 58. On the 16th hospital day, he suddenly lapsed into coma for the second time and died within 30 minutes. Unfortunately, consent for postmortem examination could not be obtained.

The diagnosis of nephrosis was based on the presence of marked albuminuria, generalized edema, hypercholesterolemia, hypoproteinemia, and low serum albumin. Death was apparently due to azotemia, as evidenced by the steady and rapid rise in the blood urea nitrogen levels.

Of particular interest in the second case is the development of fatal erysipelas in the course of the nephrotic syndrome. Infections were not uncommon before the chemotherapy era. More often, these children developed Pneumococcus infections, especially Pneumococcus peritonitis, and these were usually fatal. Recovery from erysipelas occurred more frequently than after Pneumococcus infections. The treatment of streptococcic diseases with sulfonamide drugs and antibiotic agents brought about the most amazing changes, not only in the course and prognosis of erysipelas, but also in its incidence. The disease, which was previously fairly common, has become almost a rarity.

Our case of erysipelas was unusual because of the rapidly fulminating course and failure to respond despite large doses of sulfadiazine, penicillin, chloramphenicol, tetracycline, and supportive therapy. Steroids were given only during the terminal period in the hope of overcoming the picture of shock. Steroids were not given during the first week of hospitalization because of the spontaneous response of the other cases of trimethadione nephrosis.

The occurrence of seven cases of nephrosis following the administration of trimethadione and paramethadione is sufficient evidence of a causal relationship. The first case of nephrotic syndrome following the use of trimethadione was reported by Barnett and co-workers [2] in 1948. The following are brief summaries of the cases reported in the literature.

Barnett, et al. described the case of a 16-year-old girl who had been taking trimethadione for petit mal attacks for eight months when massive edema, 4+ proteinuria, hypoproteinemia, and hypercholesterolemia appeared. Her condition improved five weeks after the drug was stopped. Treatment with trimethadione was resumed because of recurrence of petit mal attacks on two more occasions, and each time the nephrosis recurred after eight weeks.

In 1949, Briggs and Emery [3] described the case of an 8-year-old boy who developed nephrosis after 13 months of treatment with trimethadione. There was no improvement after the drug was stopped for two different periods of six and five weeks. It was restarted and given again until the boy died four months later.

Also in 1949, White [4] reported a 20-year-old man who developed a nephrotic syndrome after a 10-month course with trimethadione. The condition returned to normal six weeks after the drug was stopped.

Nabarro and Rosenheim,[5] in 1952, reported a 19-year-old girl who developed massive edema and other signs of nephrosis after two years' treatment with tridione. The condition improved rapidly after the drug was stopped.

Wren and Nutt [6] in 1953 described a 26-year-old man who had been receiving trimethadione for petit mal for two years without any apparent toxic effects. The drug was discontinued because of poor results and changed to paramethadione. After one and a half years of paramethadione therapy he developed the nephrotic syndrome. Diuresis started 10 days after the drug was stopped, and there was complete recovery in six weeks.

In 1952, Tegelaers and Tiddens [7] reported a 6-year-old boy who developed the nephrotic syndrome after a year of treatment with trimethadione for petit mal attacks. Complete cure resulted shortly after the drug was discontinued.

After the reports of trimethadione nephrosis,[8] Millechap and Kernan studied 12 children treated with trimethadione. Of these, eight showed microscopic abnormalities of the urine within eight weeks of the start of treatment. The authors concluded that microscopic urinary abnormalities were not uncommon with trimethadione therapy, and if such abnormalities were permitted to go unrecognized, they might lead to more serious kidney sequelae.

On the other hand, Denhoff, et al.[9] found occasional abnormal urines in healthy children, as well as after convulsant drugs, studied for long periods. They concluded that minor urinary abnormalities in themselves are not indicative of kidney damage.

Analysis of the reported cases of trimethadione nephrosis reveals some distinguishing features of this form of the disease. Lipid nephrosis is characterized by insidious onset, usually between the ages of 1½ and 4 years. It is comparatively a rare disease in adults. The cases reported secondary to trimethadione were in older children, aged 7 and 8 years, and three were in adults, aged 19, 20, and 26. Our two cases were of children aged 6 and 9 years. The duration of the nephrotic syndrome varies from a few weeks to a few years. Characteristic of the nephrosis due to trimethadione is that there was spontaneous recovery or death within a few weeks after onset. The only exception is the case reported by Briggs and Emery.[3] Their patient failed to develop a remission and died eight months after the onset of nephrosis. In this case, the drug was not discontinued entirely.

The pathology of nephrosis is primarily found in the basement membrane of the glomerulus. There is a thickening of the basement membranes with increase in

the number and size of the adjacent visceral epithelial cells. Occasionally, the basement membrane shows moderate splitting.[10] The glomerular tufts also undergo changes. Ehrich [11] has pointed out that if injury of the basement membrane is associated with extensive thrombosis and subsequent sclerosis of loops, or with extensive extracapillary exudation and crescent formation, or both, the patient is bound to die with progressive renal failure. If these changes are insignificant or absent, recovery may ensue. In the microscopic study of the kidney in our second case, we found evidence of marked thickening of the basement membrane around all or most of the glomerular tufts, with early scarring of the membrane in the same tufts. Since this child died rather early in the course of the nephrosis of intercurrent infection, we would not expect to see the fibrosis and scarring that would be found in the normal course of a fatal case of nephrosis.[11]

Summary

Two additional cases of trimethadione (Tridione) nephrosis are reported, making a total of seven cases. One case was reported secondary to paramethadione (Paradione), a closely related drug. Four of the cases responded spontaneously. One of the reported cases and our two cases ended fatally. Our second case had a postmortem examination and is the first pathological report of a case of trimethadione nephrosis. The pathology of nephrosis is discussed in the light of our findings.

Trimethadione nephrosis is characterized by its occurrence in older children and in adults, and by its short duration, ending in either recovery or death.

Conclusions

1. Patients treated with trimethadione and other anticonvulsant drugs should have routine urine examinations, as well as blood studies.

2. The findings of minor urinary changes in themselves are not indicative of kidney damage.

3. The drug should be stopped and appropriate measures taken when there is evidence of nephrotic syndrome.

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Intralobar Bronchopulmonary Sequestration in Children

Diagnosis by Intrathoracic Aortography

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Intralobar bronchopulmonary sequestration is a congenital pulmonary disease in which a portion of an otherwise normal lobe has no connection with the bronchial tree or pulmonary arterial circulation, and receives its arterial supply from anomalous branches of the aorta. This condition is relatively well known to radiologists and surgeons as a cause of lung cysts and recurrent infection requiring resection; but in spite of its congenital nature and the early appearance of symptoms in some patients, we have not found it reported in pediatric journals, although many cases have been described in children. Extralobar sequestration, in which the same pathological features occur in an accessory lobe, has been reported twice in newborn infants by pediatricians in surgical journals.[1,2] The purpose of this paper is to call the attention of pediatricians to intralobar sequestration and to report an effective method of proving the diagnosis by visualizing the anomalous arteries.

Incidence

Up to 1955 Bruwer[3] had tallied 10 reported autopsied cases, but this condition has rarely been found at autopsy in infants.[4-6] As of 1958, the total number of reported cases[7,8] may be estimated as at least 106. Symptoms usually appear in the first or second decade. The average age at operation was 26 in one series of cases. Both sexes have been affected with equal frequency.[8-10]

Submitted for publication Nov. 6, 1958.

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Pathology

The lesion is commoner in the left than in the right lung and most frequently occupies the posteriobasal segment of the lower lobe. The bronchi have no developmental connection with the functioning bronchial tree of the normal lung and have usually undergone extensive cystic changes. The cysts may be single or multiple and have walls composed of bronchial elements lined with respiratory epithelium. They contain mucus, pus, blood, air, or air and fluid. In some specimens connections between the cysts and bronchi of nearby segments are found; these may be secondary connections caused by erosion due to infection. The latter occurs frequently both inside the cysts and in the surrounding fibrotic tissue, which is usually inflamed. Alveoli are not present in the sequestration.[11]

The abnormal portion of the lung contains neither pulmonary arteries nor bronchial arteries but gets its arterial supply from one or more arteries which arise from the aorta above or below the diaphragm and reach the lung via the inferior pulmonary ligament. They are usually of large caliber (5-7 mm. in diameter) and have been reported almost as large as the aorta itself.[12] The walls are elastic rather than muscular, and histologically they resemble pulmonary rather than systemic arteries. Arteriosclerotic changes are often present. The vessels ramify along the bronchi when the latter are recognizable and may also supply part

of the adjacent normal pulmonary tissue. Such arteries can even exist in the absence of sequestration.[9] The venous drainage in intralobar sequestration is almost always to the pulmonary veins, although in Case 3 of Kergin[13] there was a small vein draining into the azygos vein. Drainage to the hemiazygos or other systemic veins is the rule in *extrapulmonary* sequestration.

Pathogensis

Various theories have been propounded to account for the coexistence of the pulmonary and circulatory anomalies.[6,9,14-17] They differ primarily as to whether the lung cysts are secondary to the abnormal arteries or whether the arterial supply is distorted because of anomalous development of the lungs. It seems pointless to review these controversies in detail; the soundest attitude is that of Cole et al.,[17] which is concurred in by Bruwer et al., that when something goes wrong with the embryologic development of the thoracic structures, various tissues and systems are likely to be involved.

Infection may be introduced through the bronchi when the cysts communicate with them. When there is no bronchial connection, bacteria get into the cysts by invading their walls from adjacent areas of pneumonitis or by hematogenous spread.[10]

Clinical Picture

Although the disease is sometimes discovered by routine chest survey films, the majority of patients come to operation because of repeated episodes of acute pulmonary disease, associated with intermittent cough, occasional blood-streaked sputum, fever, chills, and x-ray evidence of a pathologic process in one lower lung field. The diagnosis is often mistaken for pneumonia, empyema, bronchiectasis, or lung abscess.

Radiologic Appearance

If there is a communication with the bronchial tree, single or multiple air-fluid levels may be present in the posteriobasal segment of a lower lobe. If not, an oval density may be seen. It is usually poorly defined in the lateral view in comparison with the anteroposterior view. Fry et al.[18] believe that air may be present in the cysts due to *"metabolic gas,"* even in the absence of a bronchial connection. Both appearances may be present at different times in the same patient, depending on whether the cysts are filled with fluid or air and fluid. On bronchography the segment occupied by the lesion does not fill.

Diagnosis

It should be possible to establish the diagnosis from the characteristic findings on the plain films and bronchograms. Further efforts to prove the diagnosis prior to operation have been directed at demonstrating the presence of the abnormal artery.

Plain films sometimes give the suggestion of an anomalous vessel. Wyman and Eyler[19] point out that the long axis of the lesion is often directed medially and posteriorly toward the aorta.

The vessel has been demonstrated by *tomography* by Bruwer.[3] Landry and Salatich[20] also demonstrated two vessels in the same patient by tomography "beyond all shadow of a doubt in their entirety."

Gerard and Lyons[21] have demonstrated the artery in one case by *venous angiocardiography*. On the whole, however, angiocardiograms show only absence of pulmonary arteries in the involved area.[6]

Kenney and Eyler[22] have successfully visualized it by *aortography* performed by needle puncture of the aorta.

The method to be described here is intrathoracic aortography via a catheter.

Therapy

Almost all reported patients have been operated upon. Segmental resection is undoubtedly the only dependable means of preventing recurrent infection, although individual attacks respond to antibiotic treatment.

Fig. 1 (Case 1).—A film taken shortly after birth reveals an infiltration in the region of the left lower lobe with multiple radiolucent areas within it.

Fig. 2 (Case 1).—At age 4 months the density and radiolucent areas are again seen in the sequestered segment.

Method

We have performed aortography in two cases by the intrathoracic method which has been used for the diagnosis of congenital heart disease, chiefly in Sweden.[23] An incision was made in the right antecubital fossa under local anesthesia and the brachial artery isolated. The right arm was chosen because the route to the descending aorta forms a more gradual curve from the right than from the left arm.

The artery was opened and a slightly modified No. 6 Lehman aortographic catheter introduced and passed through the aortic arch into the descending aorta under fluoroscopic control. From 0.67 to 0.75 ml.

Fig. 3 (Case 1).—Age 12 months. The density within the sequestered lung is now seen as a well-defined homogeneous area, and the cystic areas are no longer seen.

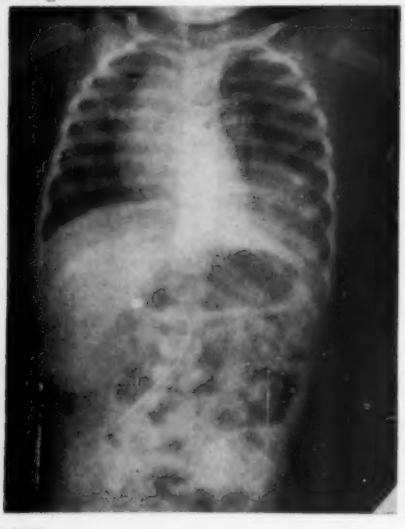


Fig. 4 (Case 1).—Age 15 months. A large cystic area is now seen in the sequestration.

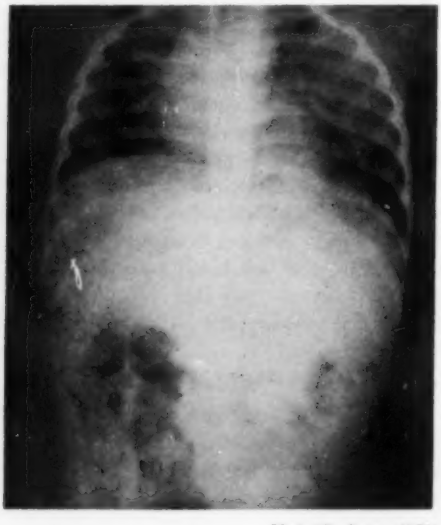


Fig. 5 (Case 1).—Age 3 years. One large and multiple small radiolucent areas are seen in the sequestered lung.

per kg. of 70% sodium acetrizoate was rapidly injected through the catheter, using a device consisting of a veterinary syringe and a hand-operated lever giving a mechanical advantage of 3:1. Six films were taken at 0.6-second intervals with the seriograph (Sanchez-Perez Automatic Seriograph). After the injection the catheter was withdrawn and the opening in the artery sutured.

Report of Cases

CASE 1.—A 6-year-old Puerto Rican girl was admitted to Kings County Hospital for a febrile illness of two weeks' duration. She had been born at another hospital in New York City, weighing 1,970 gm. A few hours after birth tachypnea and retractions were noted, and a chest film showed radiolucent areas with surrounding infiltration in the left lower lung field medially (Fig. 1). She improved on antibiotic treatment. Thereafter she had been admitted to hospitals repeatedly for fever and dyspnea with x-ray evidence of disease in the posterior basal segment of the left lower lobe (Figs. 2-4). On one such admission at age 11 months the x-ray had shown consolidation in the left lower lobe which changed to a cystic appearance after resolution of the pneumonia (Figs. 3 and 4). Between acute episodes she had had an intermittent productive cough. A film taken at age 3 years showed a radiolucent area in the left lower lobe with surrounding patchy and linear infiltration (Fig. 5).

At the time of admission, her temperature was 38.1 C (100.6 F). The patient was a thin, underdeveloped girl who appeared chronically ill. She weighed 15 kg. and was 120 cm. tall. The tonsils were inflamed and contained pus. There was an area of dullness and decreased breath sounds in the lower part of the left chest posteriorly. The

Fig. 6 (Case 1).—Age 6 years. The density in the sequestered lung is fairly well defined and is seen to be in the region of the posterior basal segment on the lateral film.

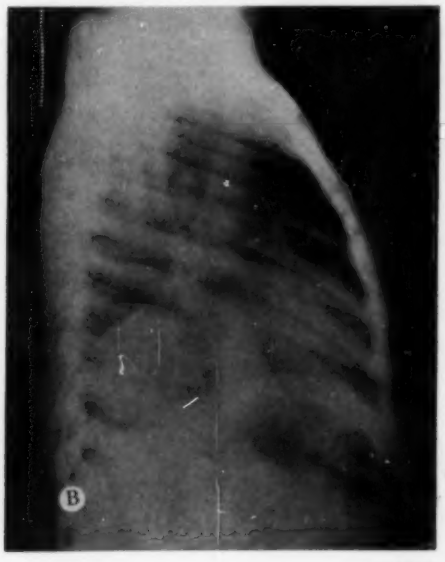
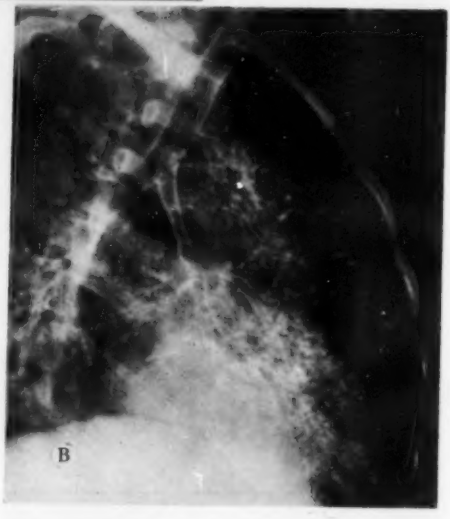


Fig. 7 (Case 1). — A bronchogram reveals displacement of the bronchi and failure to fill any bronchi in the region of the sequestration.

leukocyte count was 12,300 per cubic millimeter, with 63% polymorphonuclear cells, 32% monocytes, and 2% basophiles. A chest film showed a large area of consolidation in the left lower lobe, which appeared rounded in the posteroanterior view, but the borders of which were not well defined in the lateral view (Fig. 6, *A* and *B*). After an initial febrile period she improved clinically, and the x-ray appearance then showed one large and several small radiolucent areas within the infiltration. At bronchoscopy, the carina was found to be displaced to the right, and the left main bronchus was angulated to the left. Bronchography demonstrated absence of filling of the portion of the bronchial tree in the region of the infiltration. The visualized bronchi were intrinsically normal except for slight lateral deviation from the area of infiltration (Fig. 7, *A* and *B*). A few days later several arteries arising from the thoracic aorta and entering the cystic area in the left lower lobe were demonstrated by intrathoracic aortography (Fig. 8). On the 30th hospital day the posterior basal segment was resected. Three arteries emanating from the thoracic aorta and supplying this segment and one anomalous vein draining into the hemiazygos vein were found and ligated. This portion of the lung was occupied by a rubbery mass of multiple communicating cysts which proved to have no connection with the bronchial tree. There was one larger cavity about 3 cm. in diameter. No bronchi were present in the resected specimen, and the lung tissue surrounding the cysts was atelectatic, fibrotic, and chronically inflamed. Two of the arteries were of the elastic type and one of the muscular type.



The postoperative course was complicated by hydro- or hemopneumothorax, which resorbed spontaneously, and the patient was discharged on the 24th postoperative day.

Case 2.—A 6-year-old white boy was admitted to Kings County Hospital because of a three-day history of fever, chills, and left-sided chest pain. The history of his birth, neonatal period, and early development was normal so far as could be determined. He had been admitted to another hospital at age 1 year for left lower lobe pneumonia, at age 2 for pneumonitis, said to be due to bronchial stenosis, and at age 3 for an abscess in the left lower lobe. Since the last of these

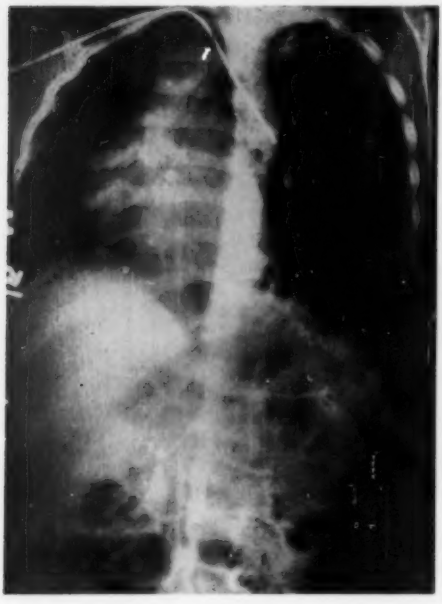


Fig. 8 (Case 1).—Aortogram. A tortuous vessel is seen arising from the lower part of the thoracic aorta and entering the sequestered lung.

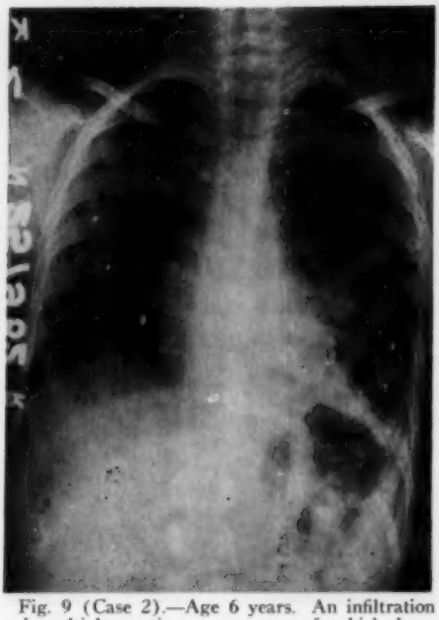


Fig. 9 (Case 2).—Age 6 years. An infiltration and multiple cystic areas, some of which have air-fluid levels within them, are seen in the region of the left lower lobe.

admissions, he had had an intermittent cough. The admission examination showed a thin pale boy with a high fever, weighing 21 kg. and measuring 123 cm. in height. The only abnormal chest findings were dullness to percussion over the left lower lobe and intermittent ronchi. There were no rales or changes in vocal fremitus. The spleen was palpable. The leukocyte count was elevated, with predominance of polymorphonuclear cells. The chest film showed many radiolucent areas in the left lower lobe surrounded by patchy and strand-like density (Fig. 9). This condition improved rapidly with antibiotic therapy. Ten days later the radiolucent areas had disappeared, leaving an oval density in the left lower lobe (Fig. 10). Inflammation and stenosis of the left basal segmental orifice were seen at bronchoscopy. On the bronchogram (Fig. 11, *A* and *B*) no bronchiectasis was found, but there was displacement of the lower lobe bronchi laterally and anteriorly, with no filling in the region of the oval mass which was situated medially and posteriorly in the left lower lobe. This appearance suggested intralobar bronchopulmonary sequestration. Venous angiocardiography had been performed previous to our study of the patient, but an aberrant artery was not definitely demonstrated. Intrathoracic aortography (Fig. 12) clearly showed a large artery about 0.5 cm. in diameter arising between the apparent level of the diaphragm and the celiac artery, following a course upward and to the left, and branching in the periphery of the pulmonary density. It was thought that its origin was below

Fig. 10 (Case 2).—Ten days after Figure 9. A well-defined area of density is seen within the sequestered lung. The cystic areas are not seen.

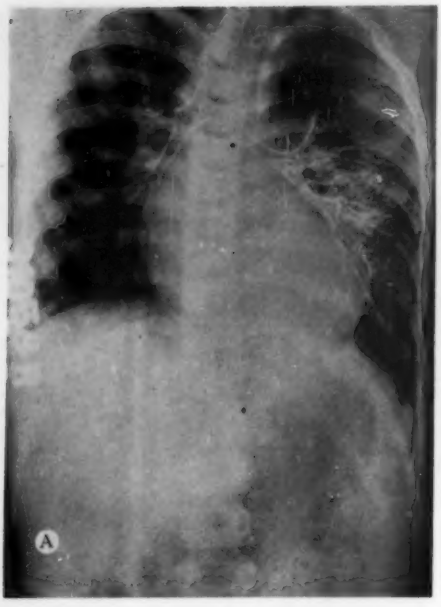


Fig. 11 (Case 2).—A bronchogram, as in Case 1, reveals displacement of the bronchi and no filling of any bronchi in the area of sequestration.

the diaphragm. At operation, a well-demarcated, poorly aerated posterior basal segment with no bronchial connection was found. The segment was supplied by an artery 1 cm. in diameter coming from the aorta above the diaphragm and drained by one large vein which could not be traced. There were thick fibrous adhesions between the involved lung and the adjacent diaphragmatic and parietal pleura. During segmental resection, many small cysts containing thick yellow pus were encountered. In the resected specimen the cysts were seen to communicate with one another. They were lined by pseudostratified ciliated columnar epithelium ulcerated in many places and enclosed in a wall of incomplete layers of smooth muscle and rather dense fibrous tissue. A small amount of fibrotic lung tissue was present. Chronic inflammatory cells were seen in the cyst contents, walls, and surrounding lung. The large artery was of the elastic type. The patient's postoperative course was satisfactory, and he was discharged on the 15th postoperative day.

Fig. 12 (Case 2).—An aortogram shows a large anomalous vessel arising from the lower portion of the thoracic aorta and entering the area of sequestration.

Comment

The diagnosis of bronchopulmonary sequestration can doubtless often be made on the basis of the history, plain films, and bronchograms.[3] Although the finger-like projection extending medially and downward from the body of the lesion described by Wyman and Eyler [10] may be helpful when present, it was not present in either of our cases. Nevertheless, the location of the involved areas in the posterior basal segment of the left lower lobe and the re-

currence of disease always in the same part of the lung were suggestive. Two findings of diagnostic importance were demonstrated in our cases. In Case 1 it was found that the radiographic abnormality had been present since birth, and in both cases changes from a solid to a cystic appearance and vice-versa were observed. It would seem that these two features are typical of intralobar bronchopulmonary sequestration, even though their diagnostic value is limited to those patients who have had serial x-rays.

Tomography was not attempted in our patients; this method of demonstrating the anomalous blood supply may be useful in adults, but adequate cooperation is not to be expected in children. Angiography has not been widely applied. Angiocardiography has been recommended recently in a publication by Gerard and Lyons,[21] including one of the cases reported here. These authors believe that angiocardiography is the method of choice for visualizing the abnormal arteries, although only one of their two cases had this procedure, the other (our Case 1, their Case 2) having been shown by aortography alone. A disadvantage of angiocardiography is that the injected solution must pass through the veins of the arm and mediastinum, the heart, pulmonary circulation, and aorta before reaching the lesion. In order to get dense opacification of the arteries entering the sequestration after the dilution that occurs en route, large doses of contrast medium must be used. Moreover, lingering opacification of the pulmonary vessels may obscure the appearance of opaque medium in the arteries arising from the aorta. Our Case 2 required aortography after angiocardiography had given unsatisfactory results.

Aortography is the most direct and effective means of demonstrating the abnormal arterial supply in bronchopulmonary sequestration. The method described above permits delivery of the contrast medium directly to the descending aorta so that there is dense filling of the systemic arteries entering the lung but not of the pulmonary arteries. Since the injected solution enters the circulation downstream from the carotid arteries, the chief danger of retrograde brachial aortography and thoracic aortography with the catheter tip at a higher position, i. e., cerebral complications, is avoided; therefore 70% rather than 30% concentration may be used. The necessity for blindly introducing needles into the aorta with the possibility of injury to nearby organs or extravasation is also obviated. Disadvantages of the method are the necessity for arteriotomy and subsequent suturing of the opening. The only complication we have observed from the intra-arterial use of cardiac or aortographic catheters in infants and children for aortography or aortic pressure measurements is loss of the radial pulse, without other evidence of circulatory deficiency, in one case.

There are two reasons why demonstration of the arteries to a sequestration may be desirable. In doubtful cases, the diagnosis may be proved in this manner. Even in typical cases, the surgeon's work may be made easier and safer by prior knowledge of the course and size of the arteries. Fatal hemorrhages have occurred at operation when this condition was not recognized preoperatively.[24]

Summary

Intralobar bronchopulmonary sequestration is a congenital anomaly of the lung causing chronic and recurrent infection and requiring surgical removal. It can be identified by the history and appearance on the plain x-rays and bronchogram or by demonstration of the abnormal systemic artery which supplies it by intrathoracic aortography or other means. Pediatricians should consider this diagnosis in cases of localized chronic or recurrent pulmonary disease.

The bronchoscopies and operations were performed by Drs. F. P. Gerard and E. H. Griffin of the Division I Thoracic Surgery Service, Kings County Hospital.

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Recognition and Treatment of Intracranial Manifestations of Leukemia

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Editorial Note: *The occurrence of intracranial complications in acute childhood leukemia has become increasingly important as more and more prolonged hematologic remissions are achieved with current methods of therapy. While the presentation of the cases tends to bring out the importance of this fact, the experience of the author is not entirely typical of that gained by the study of a larger series. Specifically, it might be well to stress that in many instances neurologic symptoms occur, sometimes repeatedly, while not only the peripheral blood but study of the bone marrow indicates a prolonged complete hematologic remission. It is also worth pointing out that by intrathecal therapy freedom from neurologic symptoms can often be maintained for longer periods than the results of this article would indicate.*

As the natural history of leukemia has been modified by induced remissions, it has become clear that increased intracranial pressure due to the leukemic process may be present for long periods of time without frank clinical manifestations, and only systematic examination of the eyegrounds and periodic checks on the pressure and composition of the spinal fluid will alert the clinician. The author's experience in one other respect is not typical of that in other clinics. We have usually found a significant elevation of the protein and a decrease in sugar initially and then a reversal of these changes under therapy. As it is now possible to maintain life up to several years, the study and treatment of the intracranial manifestations of leukemia have become important, and it would be desirable to have a dosage schedule for intrathecal therapy and to have the role of supplementary radiation more definitely established.

WOLF W. ZUELZER, M.D.

One of the prime objectives in the therapy of acute childhood leukemia is to maintain the patient symptom-free and capable of enjoying normal activity. The development of neurologic complications poses a serious threat to this aim.

Leukemia involving the central nervous system may be manifested by symptoms and signs of meningeal irritation and increased intracranial pressure, seizures, and/or cranial nerve palsies. Not infrequently patients who have had no symptoms or signs of central nervous system involvement during life may at necropsy be found to have widespread infiltrative lesions involving the meninges and brain.

Since orally administered antimetabolites apparently do not penetrate the blood-cerebrospinal fluid barrier in sufficient concentrations to prevent or control such complications, therapy in the past has included steroids and irradiation to the skull. The beneficial effects of these modes of therapy may be quite short in duration.[1]

Recently, Burchenal and co-workers [2] described a dramatic beneficial effect in five patients after the intrathecal administration of amethopterin. The present report will describe four children, one of whom presented with acute hydrocephalus, who responded quite well to this therapy.*

Submitted for publication Nov. 24, 1958.

From the Department of Pediatrics, State University of Iowa College of Medicine.

Aided by a grant from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

*The Lederle Laboratory Division of the American Cyanamid Company supplied the amethopterin as Methotrexate for parenteral use.

Procedures, Methods, and Special Studies

Four children with acute lymphocytic leukemia were studied in whom signs and symptoms of central nervous system involvement occurred during the course of the disease. Serial examinations of the cerebrospinal fluid were performed in conjunction with the intrathecal administration of varying doses of amethopterin. Lumbar punctures were performed at the level of L4-L5. Two to four milliliters of cerebrospinal fluid was removed and used as diluent for the amethopterin. The latter was then directly instilled into the subarachnoid space during an interval of three minutes. The studies of the cerebrospinal fluid included estimation of pressure, number of cells, with special emphasis on the cytology, protein content, sugar content, bacterial, fungal, and viral cultures, and bioassays for amethopterin content.

The amethopterin assays on the cerebrospinal fluid were performed by the method of Burchenal.[2,3] Cerebrospinal fluid and solutions containing known amounts of amethopterin† were delivered to penicillin assay discs on an agar plate containing Difco folic acid medium, 1 mg. per milliliter of pteroylglutamic acid,† and Streptococcus faecalis (ATCC 8043). After incubation at 37 C for 24 hours, the zones of inhibition around each disc were read with a Fisher-Lilly antibiotic zone reader. The size of the zone of inhibition around the specimen of cerebrospinal fluid obtained from the patient was compared with that around equal volumes of solution containing known concentrations of amethopterin.

Laboratory Results

The initial cerebrospinal fluid findings in the four patients are summarized in Table 1. The most consistent finding was increase in white blood cells which were predominantly mononuclear in type. The cells were large and many contained easily demonstrable nucleoli. The patients in this study did not have significantly altered protein and sugar contents in the cerebrospinal fluid before therapy. The cultures for bacterial, fungal, and viral agents yielded no growth.

By the bioassay method employed, amethopterin could be detected in the cerebrospinal fluid of the patients studied consistently in levels of 20 to 60 mμg. per milliliter for three days. In only two patients on two occasions was it possible to detect any amethopterin activity as long as five days after its intrathecal administration.

Report of Cases

CASE 1.—A 16-month-old girl was first admitted to University Hospital on March 2, 1958. The child had been in good health until six weeks before admission, when she fell and struck her head. After this, the patient had progressive symptoms, including swelling about both eyes, increasing irritability, anorexia, lethargy, swelling of the gums, and an increasing prominence of the superficial veins of the scalp. During the month preceding admission, she was treated with antihistamines and antibiotics without benefit. There had been progressive enlargement of the head circumference in the two weeks preceding admission.

Physical examination at time of admission revealed normal blood pressure, temperature of 100 F rectally, and respirations of 32 per minute. The child appeared to be acutely uncomfortable and in pain. The upper portion of the face was swollen with brawny, nonpitting edema. The superficial veins of the scalp were distended. There was bilateral exophthalmos. The fronto-occipital circumference of the head was 53 cm. All suture lines were spread and tense. The ocular fundi were normal. There was generalized hypertrophy of the gingivae. There was moderate cervical lymphadenopathy. The gait was unsteady and wide-based. There was truncal ataxia. The deep tendon reflexes were symmetrical and equally active bilaterally.

† These substances were supplied by Dr. J. M. Ruegsegger of the Lederle Laboratory Division of the American Cyanamid Company.

TABLE 1.—*Initial Cerebrospinal Fluid Findings in Patients with Intracranial Leukemia*

Case	Pressure	Cells * (Number/ Cu. Mm.)	Blasts	Protein (Mg/100 Ml.)	Sugar (Mg/100 Ml.)	Cultures	
						Bacterial	Viral
1	Elevated	37	+	33	51	0	0
2	Normal	250	+	28	41	0	0
3	Elevated	100	+	23	40	0	0
4	Normal	30	+	32	48	0	0

* Predominantly mononuclear cells in all cases.

Fig. 1.—Roentgenogram of the skull showing spreading of the sutures in Patient 1.

Fig. 2.—Roentgenogram of the skull after instillation of 30 ml. of air into the subdural space in Patient 1.

Laboratory studies: The hemoglobin concentration was 8 gm. per 100 ml. The leukocyte count was 32,000, with a differential revealing 28% blast forms, 37% lymphocytes, 26% polymorphonuclear cells, 4% nucleated red blood cells, 2% basophils, and 3% monocytes. The bone marrow contained 74% lymphoblasts, 7% lymphoid elements, 5% myeloid cells, and 14% erythroid cells. The platelets were adequate. The erythrocyte sedimentation rate (Westergren method) was 32 mm. per hour. Roentgenograms of the skull showed marked spreading of the sutures consistent with increased intracranial pressure (Fig. 1). Roentgenogram of the chest revealed bilateral pleural effusions and hilar lymphadenopathy. A subdural tap was performed, and xanthochromic fluid was removed which contained 30,000 fresh red blood cells per milliliter. After removal of the subdural fluid, 30 cc. of air was injected into each subdural space in order to confirm the location of the fluid (Fig. 2). Cultures of the subdural fluid for virus and bacterial agents yielded no growth. The protein content of the subdural fluid was 470 mg. per 100 ml. A thoracentesis was performed and 50 ml. of cloudy serous fluid was removed from the left pleural space. The cytologic examination of both the subdural and pleural fluids revealed many lymphoblasts. The cerebrospinal fluid pressure was elevated. There were 37 large mononuclear cells per cubic millimeter, many of which were blast cells. The protein and sugar contents of the cerebrospinal fluid were normal (Table 2).

After the diagnosis of acute lymphocytic leukemia was established, prednisone was administered orally. At the same time, amethopterin was given intrathecally on days 1, 5, and 10. On the first administration, 2.5 mg. of amethopterin was given intrathecally between L4 and L5 and another 2.5 mg was instilled into the subdural space (0.40 mg. per kilogram). There was prompt clinical improvement, and within three days the

TABLE 2.—*Cerebrospinal Fluid Examinations in Patient 1*

Cerebrospinal fluid	3/3	3/7 *	3/10	3/12 *	3/17 *	4/4	4/25 *	4/30 *	6/13	6/20	7/15 †
Opening pressure	320	—	130	N	N	230	240	N	N	550	
Cells (number/cu. mm.)	37	40	920	2·0	5	0	5	0		5	
Blasts	+	+	+	+	0	0	+	0	0	0	
Protein (mg/100 ml.)	33	33	43	69	22	19	27	26	22	31	
Sugar (mg/100 ml.)	51	71	60	78	74	83	57	47	44	44	
Chloride (mEq/liter)	121	114	—	—	—	—	117	—		—	
Virus and bacterial cultures	0	0	0	0	0	—	—	—	0	0	
Blasts in bone marrow (%)	74				60	45	71		80	95	
	Steroids				6-MP		Amethopterin				

* Amethopterin (intrathecal).

† Several attempts to obtain CSF at L4-5 were unsuccessful.

child was eating well and was without fever. The head size diminished from 53 cm. to 50 cm. within four days. Although all signs and symptoms of central nervous system involvement subsided, the peripheral white blood cell count and bone marrow never showed evidence of more than a moderate remission during therapy with steroids. Accordingly, on March 25, 1958, 6-mercaptopurine was added to the therapy, and the dosage of prednisone was decreased and finally discontinued.

The patient was readmitted to University Hospitals on April 25 because of anorexia and frequent vomiting. It was found that the circumference of the head had increased from 49.5 cm. at time of discharge to 51.5 cm. Examination of the bone marrow showed 71% blast forms. Accordingly, the child was admitted and given another course of amethopterin intrathecally, to which she again responded quite dramatically. In addition, 2.5 mg. of amethopterin was given orally each day. After cessation of symptoms, the patient was discharged.

Readmission was necessary on July 15, 1958, because of recurrence of signs and symptoms suggesting increased intracranial pressure. On repeated lumbar punctures, no cerebrospinal fluid was obtained. It was postulated that there was a block due to leukemic infiltrate preventing cerebrospinal fluid from entering the spinal canal. For this reason, irradiation therapy to the skull was employed. This was administered in a total dose of 400 r over a five-day period. There was a rather dramatic response to this therapy clinically, and she was discharged on Aug. 27.

The patient was readmitted for the last time on Sept. 2 with bilateral pleural effusions, pulmonary infiltrate, and rapid, shallow respirations. She died on Sept. 4, 1958.

Necropsy findings: There were extensive leukemic infiltrates in the skin, pleura, lung parenchyma, lymph nodes, liver, and kidneys. A subdural membrane, which seemed to be contiguous with the sutures and which was heavily infiltrated with leukemic cells, was present. There were perivascular infiltrates in the leptomeninges. The cerebral hemispheres were moderately edematous but contained neither infiltrates nor hemorrhages.

Comment on Case 1.—The onset of acute leukemia is quite varied. The present case demonstrates an unusual initial manifestation, i. e., acute hydrocephalus.

The complete remission of central nervous system manifestations of leukemia achieved on the first admission must be attributed to the joint action of steroids and intrathecal amethopterin since they were administered simultaneously. However, the remission obtained after the second exacerbation of central nervous system disease can be attributed solely to the action of amethopterin administered intrathecally.

Since other intrapulmonary neoplasms are prone to metastasize to the brain, it is interesting to note that there was coexisting intrapulmonary and intracranial leukemia in this patient at time of admission.

A summmary of cerebrospinal fluid findings in relation to bone marrow status and therapy is given in Table 2.

CASE 2.—A 9-month-old infant was admitted to University Hospital on March 18, 1958. The neonatal period had been uneventful, with no jaundice, cyanosis, or difficulty with feedings. Because the mother of the patient had had acute lymphocytic leukemia during the pregnancy and had died from that disease, the patient was observed quite carefully.[4] At one week of age, a complete blood count did not reveal any abnormalities. The child was always content, vigorous, playful, and ate well. There were no periods of unexplained fever. One week before admission, the patient became irritable and anorexic. Two days before admission, the child started developing petechiae, ecchymoses, and purpuric areas. On the day before admission, the family physician examined the child and noted the hemorrhagic manifestations. In addition, he also found that the liver and spleen were enlarged.

At the time of admission, the temperature was 100.6 F. The child was well developed but pale and irritable. He had petechiae, ecchymoses, and purpuric areas scattered over the skin of the trunk, extremities, and skull. Petechiae were also noted on the mucous membranes of the soft and hard palates and buccal mucosa. The lymph nodes were not enlarged. The inferior margin of the liver was palpated 4 cm. below the right costal margin. The inferior margin of the spleen was palpated 7 cm. below the left costal margin. Both organs were firm in consistency.

Laboratory studies: The concentration of hemoglobin in the blood was 9.6 gm. per 100 ml., and the leukocyte count was 46,000. The differential count revealed 92% lymphocytic forms, most of which were immature and blast forms. The platelet count was 6,000. Examination of the bone marrow revealed 91% blast forms, 6% lymphocytes, 2% monocytes, and 1% erythroid elements with a paucity of platelets. Roentgenograms of the chest, skull, and long bones did not reveal any abnormality.

As soon as the diagnosis of acute lymphocytic leukemia was established, prednisone (40 mg. per day) was administered. Although the size of the spleen decreased, there was no evidence of re-

TABLE 3.—*Cerebrospinal Fluid Examinations in Patient 2*

Cerebrospinal fluid	6/6	6/18 *	6/23 *	6/28 *	7/11	8/7
Opening pressure	150	Inc.	N	N	N	N
Cells (number/cu. mm.)	250	1,000	70	2	0	2
Blasts	+	+	+	0	0	0
Protein (mg/100 ml.)	28	30	52	52	34	27
Sugar (mg/100 ml.)	41	28	44	42	61	48
Chloride (mEq/liter)	—	—	—	—	—	—
Virus and bacterial cultures	0	0	0	0	0	0
Blasts in bone marrow (%)	6				81	
Oral therapy	Amethopterin				Prednisone	

* Amethopterin (intrathecal).

mission of the disease by examination of the bone marrow or peripheral blood. There were two episodes of rather massive gastrointestinal bleeding which were treated successfully with transfusions of fresh blood. When it became obvious that the patient was not going to respond to steroids, 6-mercaptopurine and 6-diazo-5-oxo-L-norleucine (DON) were given. With this therapy, a partial hematologic and complete clinical remission was obtained.

The child remained well until the latter part of May, 1958, when he began to bruise spontaneously. He was readmitted to University Hospital for the second time on June 6. The blood count and bone marrow examination at that time were within normal limits even though there were ecchymoses on the skin of the lower extremities. A lumbar puncture was performed on this admission, and the results are listed in Table 3. The only abnormality noted was a total white blood cell count of 250 per cubic millimeter of cerebrospinal fluid. Many of these cells were blast forms. Because there were no central nervous system signs or symptoms and because the peripheral disease seemed to be in remission, no specific therapy was instituted for the central nervous system complication.

The 6-mercaptopurine and DON were discontinued, and the patient was given amethopterin, 1.25 mg. per day. During the next few days, episodes of nausea, vomiting, and intermittent attacks of cyanosis occurred.

The patient was readmitted for the third time on June 17. The child appeared pale and was quite irritable. The head circumference had increased 2.5 cm. since the admission one month previously. Examination of the cerebrospinal fluid revealed 1,000 mononuclear cells per cubic millimeter, many of which were blast or immature lymphocytes. Roentgenographic examination of the skull revealed definite spreading of the sutures consistent with increased intracranial pressure. Accordingly, the child was given three courses of amethopterin intrathecally, 5 mg. each time on June 18, 23, and 28. This represented a dosage of 0.46 mg. per kilogram per intrathecal administration. There was prompt clinical response to this therapy, and 10 days after the first injection the cell content of the cerebrospinal fluid was normal (Table 3). The patient was asymptomatic, and roentgenograms of the skull showed decrease in the degree of separation of the sutures.

The patient remained free of central nervous system signs and symptoms until death. Two subsequent examinations of the cerebrospinal fluid on July 1 and Aug. 7 revealed no abnormalities. The child died on Aug. 14, 1958, after a massive gastrointestinal hemorrhage.

Necropsy findings: There was massive infiltration of lymphoblastic cells in lymph nodes, spleen, liver, and bone marrow. The kidneys also contained leukemic infiltrates. Examination of the brain and meninges revealed thickening of the dura secondary to leukemic infiltration, with small areas of hemorrhage. The leptomeninges were also infilterated rather extensively with leukemic cells over both cerebrum and cerebellum. Areas of hemorrhage adjacent to areas of infiltrate were common. The brain substance itself showed rather severe edema, and there were scattered areas of petechiae in both the gray and the white matter. There were larger areas of hemorrhage at the bases of the lateral ventricles. There was no evidence of chemical meningitis.

Comment on Case 2.—This patient was of great interest initially because he was the first infant born of a mother with leukemia during pregnancy who developed the same disease during the first year of life.[4]

This case also illustrates the point that intracranial leukemia may develop and flourish while the disease peripherally is in remission (Table 3).

CASE 3.—A 4 $^{10}/_{12}$-year-old boy was first admitted to University Hospital on Dec. 12, 1957. The patient had been well until the preceding September, when he became febrile and listless, and complained of abdominal pain. He was found to be "anemic" and was transfused. The patient subsequently became asymptomatic and remained well until

nine days before admission. At that time, he complained of pain in the left arm and right leg and refused to walk.

On physical examination at the time of admission there was moderate cervical, axillary, and inguinal lymphadenopathy. There were generalized petechiae and ecchymoses. The liver and spleen were palpable 4 cm. and 6 cm., respectively, below the costal margins in the midclavicular line.

The hemoglobin concentration of the blood was 8.6 gm. per 100 ml. The leukocyte count was 37,000. The differential revealed 100% lymphocytes, many of which were immature and blast forms. The platelet count was 44,000. A bone marrow aspiration revealed 95% lymphoblasts. The uric acid was 5.2 mg per 100 ml.

After the diagnosis of acute lymphocytic leukemia had been established, the patient was given 6-mercaptopurine in a dosage of 6.6 mg. per kilogram per day for two weeks, after which the 6-mercaptopurine was decreased to 2.5 mg. per kilogram per day.

A complete remission of the acute leukemia occurred with this therapy, and the patient enjoyed good health until March, 1958. At that time, the patient began to experience severe, persistent headache, and was irritable. He became anorexic and vomited two or three times each morning. The patient was readmitted to University Hospital for the second time March 13, 1958. There was minimal papilledema bilaterally. The remainder of the physical examination did not reveal any abnormalities. The peripheral blood count was normal. A bone marrow aspiration revealed 15% lymphoblasts. The opening pressure of the cerebrospinal fluid was greater than 450 mm. of cerebrospinal fluid. The fluid was clear and colorless; it contained 190 mononuclear cells per cubic millimeter, many of which were blast cells. The protein and sugar concentrations were 23 and 40 mg. per 100 ml. respectively. Cultures for bacteria, fungi, and viruses yielded no growth (Table 4).

Administration of 6-mercaptopurine was discontinued. Amethopterin was given orally in a dosage of 2.5 mg. per day. In addition, 5 mg. of intrathecal amethopterin (0.3 mg. per kilogram) was administered stat. and again on days 5 and 10. There was dramatic clinical improvement. The cerebrospinal fluid was examined frequently and rapidly became normal (Table 4).

The patient was discharged on March 26, 1958, and was observed periodically in the outpatient clinic. The child remained well until June 12, 1958, when he was admitted to University Hospital for the third time with icterus. The diagnosis of homologous serum hepatitis was made, and he was discharged two days later.

The child remained well until July 14, 1958, when he began to complain of morning headaches. Cerebrospinal fluid examinations on July 16 and July 31 showed increasing numbers of mononuclear cells, many of which were blast cells (Table 4). The patient was readmitted to University Hospital on July 31, 1958, and again three intrathecal injections of amethopterin (0.3 mg. per kilogram) at five-day intervals were given. As before, the patient responded rapidly clinically, and the cerebrospinal fluid was normal when examined 10 days after the first intrathecal administration of amethopterin. The bone marrow contained 40% blast cells, which indicated relapse of the acute leukemia. Accordingly, the amethopterin was discontinued, and he was given a combination of 6-mercaptopurine and O-diazoacetyl-L-serine (Azaserine). The patient was discharged Aug. 10.

The child was seen in the outpatient clinic on August 25. At that time the bone marrow was hypocellular. Accordingly, the 6-mercaptopurine and Azaserine were discontinued and prednisone was started in an initial amount of 40 mg. per day. A complete clinical and hematologic remission occurred. The patient was then lost to follow-up.

CASE 4.—A 4½-year-old boy was admitted to University Hospital Aug. 1, 1958. The patient had been well until four weeks previously when a gradually enlarging mass was noted on the right maxilla. The patient had had no other symptoms. At time of admission, physical examination revealed a nontender tumor mass overlying the right maxilla. There was also a large ulcerating lesion about 2.5 cm. in diameter on the hard palate immediately inferior to the right maxillary sinus. The he-

TABLE 4.—*Cerebrospinal Fluid Examinations in Patient 3*

Cerebrospinal fluid	3/13 *	3/15	3/18 *	3/20 *	3/25	4/28	6/12	7/16	7/31 *	8/5 *	8/10 *	8/25
Opening pressure	450	300	300	300	290	100	160	220	230	N	N	N
Cells (number/cu. mm.)	190	297	226	96	10	0	0	50	134	58	0	2
Blasts	+	+	+	0	0	0	0	+	+	+	0	0
Protein (mg/100 ml.)	23	27	20	29	30	31	17	20	28	74	30	28
Sugar (mg/100 ml.)	40	44	30	38	47	53	44	50	51	66	50	52
Chloride (mEq/liter)	125	120	—	—	120	—	—	129	128	170	—	—
Virus and bacterial cultures	0	0	0	0	0	0	0	0	0	0	0	0
Blasts in bone marrow (%)	15				5	2		13	74			
Oral therapy	6MP	Amethopterin							6MP + Azaserine			Steroids

* Amethopterin (intrathecal).

moglobin was 11.5 gm. per 100 ml., and the white count was 12,000. The differential was normal with the exception of one unclassified cell. A biopsy of the lesion of the right maxilla was compatible with the diagnosis of lymphoblastic lymphoma. Accordingly, this area was irradiated, and the mass became smaller. A bone marrow aspiration was performed, and this revealed 95% lymphoblasts and immature lymphocytes. The diagnosis of acute lymphocytic leukemia was made, and the patient was then started on 6-mercaptopurine and DON. During the next week, the patient's condition deteriorated. The liver, spleen, and lymph nodes all became larger. In addition, the patient became lethargic, started vomiting, and complained of headache. The child then developed episodes of twitching of both sides of the face and unconsciousness. The neurologic examination revealed bilateral Babinski responses. He also demonstrated horizontal nystagmus. On Sept. 8, 1958, a lumbar puncture was performed. Examination of the cerebrospinal fluid revealed 30 mononuclear cells per cubic millimeter, many of which were immature blast forms. Accordingly, the patient was given 5 mg. of intrathecal amethopterin (0.33 mg. per kilogram). Five days later, a bone marrow aspiration was performed and this revealed marked hypocellularity of the marrow content. For this reason, the 6-mercaptopurine and DON were discontinued. It was also decided to discontinue the intrathecal amethopterin until the cellularity of marrow increased. There was, however, dramatic improvement of the neurologic signs and symptoms after the single intrathecal administration of amethopterin. The patient was discharged on Sept. 24.

The child was readmitted for the second time on Oct. 3 with complaints of intractable vomiting and headache. A repeat lumbar puncture yielded fluid which again contained blast cells and also elevated protein content (Table 5). The child was again given 5 mg. of intrathecal amethopterin (0.33 mg. per kilogram). The peripheral disease at this point was uncontrolled and the patient became progressively moribund. He died Oct. 10, 1958.

Permission for autopsy was not obtained.

TABLE 5.—*Cerebrospinal Fluid Examinations in Patient 4*

Cerebrospinal fluid	9/8 *	10/3 *	10/7 †
Opening pressure	130	160	
Cells (number/cu. mm.)	30	30	
Blasts	+	+	
Protein (mg/100 ml.)	32	75	
Sugar (mg/100 ml.)	48	—	
Chloride (mEq/liter)	—	—	
Virus and bacterial cultures	0	0	
Blasts in bone marrow (%)	95	87	
Oral therapy	6MP	DON	Steroids

* Amethopterin (intrathecal).

† Repeated attempts to obtain cerebrospinal fluid at L4-5 were unsuccessful.

Comment

The pathogenesis of intracranial manifestations of leukemia is unsettled. It may either be the result of metastatic spread of leukemic cells from the peripheral blood and bone marrow, or else it may be the result of leukemic changes of normal cells within the central nervous system. The progress of the intracranial infiltrates does not always parallel the stage of the disease peripherally. It is not uncommon to have the onset and progression of neurologic complications while there is otherwise clinical and hematologic remission.

The manifestations of intracranial leukemia are the result of the infiltrative lesions, which are often accompanied by secondary necrosis and hemorrhage. Quite frequently the signs and symptoms are secondary to increased intracranial pressure. These include vomiting, headache, blurring of vision, seizures, and papilledema. One of the patients described in this report (Case 1) presented with acute hydrocephalus, which was found to be due to a large subdural hematoma. It is postulated that, in this particular patient, leukemic infiltrates around the vessel walls of the meninges had so weakened them that moderate trauma to the skull caused them to rupture, with resulting hemorrhage into the subdural space.

The cerebrospinal fluid pressure in such patients may be normal or elevated. The most consistent finding in the cerebrospinal fluid of the patients reported here was an increase in cells which were predominantly mononuclear and many of which were blast forms. The protein and sugar contents in these patients were initially normal, although the protein content became elevated during treatment in all of the patients. Other investigators have reported depressed sugar contents.[1,5,6] A possible explanation for this is that our patients were diagnosed and treated earlier than those reported in the

literature. Further differences in sugar content of the cerebrospinal fluid could be explained on the degree of involvement of the leptomeninges. Cultures for bacteria and viruses in these patients did not at any time yield growth.

Therapy of intracranial leukemia in the past has consisted of administration of steroids and irradiation. Steroids are effective if the patient has not received them previously and if his disease has not become resistant to them. In a critically ill patient, hydrocortisone intravenously may produce a rapid beneficial effect. Likewise, irradiation to the skull will produce remission in the neurologic disease. However, all too often, the beneficial effects are short in duration. Increasing resistance to irradiation on subsequent occasions is the usual circumstance.

The first chemotherapeutic agent to be given intrathecally for intracranial leukemia was aminopterin.[7] With this therapy, which consisted of 0.025 mg. for two days and 0.036 mg. for six days, a decrease in the leukocyte count of the cerebrospinal fluid was obtained. Burchenal and co-workers [1] were the first to describe the beneficial effects of intrathecal amethopterin.

Five patients with neurologic symptoms due to leukemia and lymphosarcoma improved markedly on 0.1 to 0.5 mg. per kilogram intrathecally. The present report, in which four patients were similarly treated, substantiates their findings. The amethopterin dosage in our patients varied from 0.30 to 0.46 mg. per kilogram and was given ordinarily on days 1, 5, and 10. There were no immediate undesirable side-effects noted in relation to this therapy.

Summary

Four patients with intracranial manifestations of acute leukemia who responded dramatically to intrathecal amethopterin are described. The results of bioassays of cerebrospinal fluid for amethopterin content are given. The changes in cerebrospinal fluid in relation to therapy are summarized.

I am indebted to the resident physicians who cared for the patients described in this report and who assisted in many of the studies. They include Drs. George Owen, Samir Najjar, and Stanley Graven. The technical assistance of Mrs. Imogene Jenson and Mr. F. David Wilkin is appreciated.

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Pseudohypo-Adrenalocorticism

Renal Sodium Loss, Hyponatremia, and Hyperkalemia Due to a Renal Tubular Insensitivity to Mineralocorticoids

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Recently many clinical syndromes have been described, characterized by renal tubular dysfunction as a major disturbance.[1-7] In some cases, tubular reabsorption of single substances is defective, e. g., water, glucose, amino acids, or phosphorus. In others, deficient reabsorption affects several materials, usually combinations of those enumerated.

Loss of cation is rare as a primary or isolated defect in tubular absorption, although it is not uncommon in association with other absorptive defects.[7] Severe depletion of calcium and potassium has occurred on numerous occasions, but loss of sodium under similar circumstances is infrequent. Salt wasting is encountered chiefly in association with advanced renal disease,[8,9] with adrenal insufficiency,[10,11] and with prolonged administration of mercurial diuretics.[12,13] Excessive excretion of sodium due to an isolated tubular dysfunction has long been postulated, but it has only recently been reported for the first time.[14]

The purpose of this paper is to present studies conducted over more than two years on an infant with a salt-losing renal tubular defect resulting in a syndrome clinically indistinguishable from Addison's disease. The data indicate that renal tubular insensitivity to aldosterone is responsible for the salt loss. Furthermore, this defect provided a unique opportunity to study certain interrelationships between sodium and potassium in the renal tubule.

Submitted for publication Jan. 26, 1959.

Fellow of the del Amo Foundation (Dr. Roldan).

Supported in part by a grant from Mead Johnson & Company, Evansville, Ind.

From the Department of Pediatrics, University of Southern California School of Medicine, the Childrens Hospital Society of Los Angeles and the Children's Medical Group (Dr. Litman).

Report of a Case

First Hospital Admission.—In May, 1956, a 7-month-old Caucasian male infant was admitted to the Childrens Hospital of Los Angeles with complaints of failure to thrive and chronic eczema. He was the fifth child of healthy young parents and the product of a normal full-term pregnancy. There was no consanguinity, and all siblings were living and well. Delivery was uncomplicated, and the infant weighed 8 lb. 1 oz. (3,660 gm.) at birth. Feedings of diluted whole cow's milk were begun on the first day of life. Two days later a liquid soya formula was substituted because of vomiting. Solid foods were started at 1 week of age and vitamins at 2½ weeks. At 2 weeks of age an erythematous, scaly rash appeared on both cheeks and spread rapidly to scalp and body. The formula was changed to evaporated goat's milk and water. Growth and weight gain were slow, although feedings were said to have been well accepted, with only occasional emesis. At 5 months of age feedings were changed to homogenized goat's milk, also without benefit. The rash which had appeared at 2 weeks of age waxed and waned under treatment with innumerable ointments.

Initial physical examination revealed a small, irritable, dehydrated boy with a widespread eczematoid rash involving the scalp, face, and flexor surfaces of the extremities. He weighed 8 lb. 8 oz. (3,855 gm.). Blood pressure was normal. The upper respiratory tract was free of infection. Coarse rhonchi were heard throughout the chest. The abdomen was protuberant, and hard fecal masses were palpated throughout the transverse and descending colon and the rectum. The genital organs appeared normal for age. Developmentally, the infant was grossly retarded. Muscle tone was generally reduced, and deep tendon reflexes were hypoactive. He supported his head but failed to sit without support. He seemed apathetic and uninterested in his surroundings. He was able to follow objects with his gaze, but made no effort to reach for them. The laboratory findings at the

time of hospital admission are summarized in Table 1.

The course of the first hospital admission is depicted graphically in Figure 1. Initial laboratory data suggested the salt-losing form of congenital adrenal hyperplasia. Accordingly, therapy was instituted to supply water, salt, and desoxycorticosterone acetate (DOCA). Parenteral fluids and desoxycorticosterone acetate were continued with gradual improvement in the state of hydration, a coincident rise in the serum sodium, and a decline in the serum potassium during a three-week period (Fig. 1). After the initial improvement, his general condition gradually deteriorated, and the serum sodium fell. This was associated with recurrence of dehydration despite continued extra water, salt, and desoxycorticosterone acetate. During this period, further study revealed markedly retarded bone age (Table 4), normal circulating 17-hydroxycorticosteroids (17-OHCS), and normal

TABLE 1.—*Initial Laboratory Findings*

Blood		
Hemoglobin (gm. %)		12.2
White blood count		28,500
CO_2 content	(mEq/L.)	19
Serum Na	(mEq/L.)	119
Serum K	(mEq/L.)	6.4
Serum Cl	(mEq/L.)	86
Serum Ca	(mEq/L.)	10.8
Serum phosphorus (mg. %)		4.7
NPN (mg. %)		31
Fasting blood sugar (mg. %)		87
Albumin (gm. %)		4.3
Globulin (gm. %)		2.3
Urine		
pH		5.0
Specific gravity		1.022
Microscopic		Negative
Albumin		0

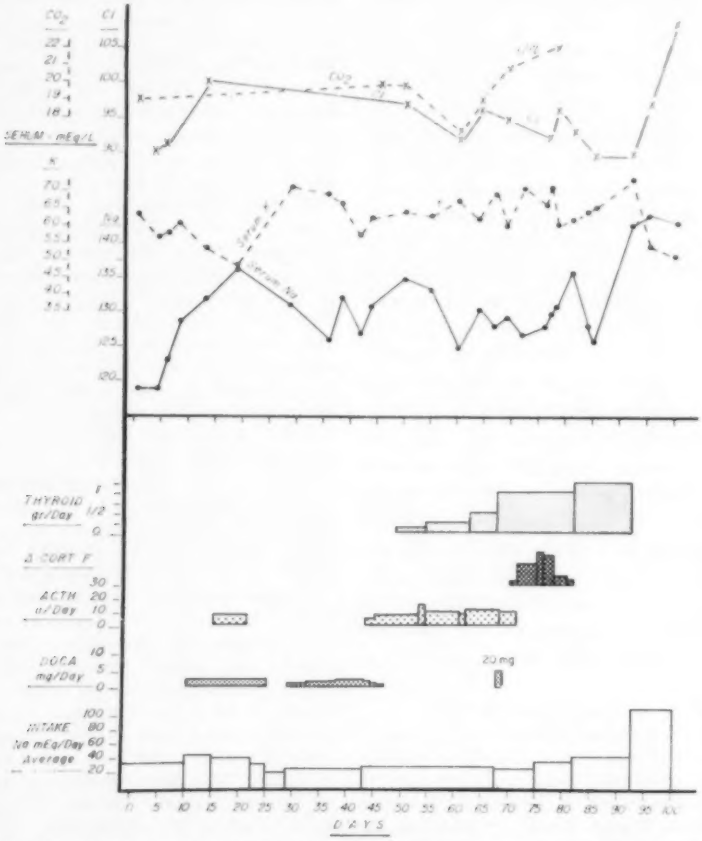

Fig. 1.—Course of the first hospital admission depicting serum electrolyte changes in response to varying forms of therapy.

TABLE 2.—*Adrenal Evaluation*

A. ACTH tolerance (6 units q. 6 hr. for 4 days I. M.)				
	Date	Steroid	Before	After
	May, 1956	Urine 17-KS	0.5 mg/day	2.2 mg/day
		Urine 17-ketogenics	1.5 mg/day	15.3 mg/day
		Plasma 17-OHCS	24μg. %	120μg. %
		Eosinophils	1,473/cm.	22/cm.
B. Urinary electrolyte response to ACTH, DOCA, and 2-methyl-9α-fluorohydrocortisone (Figs. 6, 7, and 8)				
C. Aldosterone excretion (Figs. 3 and 4)				
D. Sweat chloride			12-14 mEq/L.	

TABLE 3.—*Thyroid Evaluation*

A. Protein-bound iodine (μg. %)

Age, Mo.	Level	Comment
8	13.1	Iodochlorhydroxyquin cream
8 ½	7.3	Thyroid started at 8 mo.
11 ½	3.3	Off thyroid 4 wk.
16	6.3	
23	6.1	
31	8.8	Off thyroid 6 mo.
35	5.8	Off thyroid 10 mo.

B. I^{131} (Dose 2μc. orally)

Age, Mo.	Before	After (4-5μ/TSH/daily ×4)
8 ½	11.4%	
8 ½	8.6%	31.4%
12	4.3%	
24	12.2%	

excretion of urinary 17-ketosteroids (17-KS) (Table 2). These findings were not consistent with adrenal hyperplasia and suggested hypofunction of the adrenals either primary or secondary to failure of the pituitary.

Corticortropin gel 10 units was administered daily intramuscularly to test the response of the adrenal and to determine its effect on the salt loss. The effectiveness of corticotropin was noted clinically and by laboratory study. Appetite increased, and moon facies developed. The eosinophil count fell significantly and circulating 17-hydroxycorticosteroids and urinary steroid concentration rose accordingly. Despite the pronounced clinical effect of corticotropin (ACTH), serum sodium and potassium values changed little. Primary adrenal hypofunction seemed unlikely from these results. Except for the normal serum 17-hydroxycorticosteroid concentration, the findings were compatible with adrenal insufficiency secondary to pituitary hypofunction. Other factors favoring pituitary hypofunction at this time were growth failure, retarded skeletal maturation, and suggestive secondary hypothyroidism. The sella turcica was normal in x-rays of the skull.

Studies of thyroid function are summarized in Table 3. The initial serum protein-bound iodine was 13.1μ gm. %, reflecting the prolonged use of iodochlorhydroxyquin (Vioform) cream. It declined as low as 3.3μ gm. % after this medication was discontinued. Initial measurements of I^{131} were low (11.4% and 8.1%); after the administration of thyroid-stimulating hormone (TSH), I^{131} uptake rose to 31.4%.

X-rays of the long bones revealed generalized demineralization. Skeletal maturation at 7 months of age was essentially that of a newborn (Table 4).

Thyroid was prescribed in increasing doses until the total daily dose was 1¼ grains (75 mg.) of thyroid, U. S. P. The dose was increased slowly in order to minimize the possibility of an adrenal crisis. Little direct effect was noted from thyroid. The general improvement was attributed primarily to the replacement of water and salt.

After two and a half months of hospitalization, it was clear that his clinical course would not improve significantly without further addition of salt to the diet. Large amounts of salt were then given in an attempt to alter the apparent negative balance. Sodium chloride 85 mEq. and later sodium citrate 80 mEq. were added to the daily diet. Hydration improved, and the serum sodium gradually rose to normal. (Fig. 1).

Throughout the first hospitalization, constipation was severe. At first repeated enemas and later regular doses of milk of magnesia were necessary to clear the colon. Barium enema revealed no abnormality. The difficulty subsided with correction of electrolyte imbalance. As his general condition improved, he learned to sit alone, pull himself to a standing position, and feed himself. The eczematoid rash improved markedly. He was discharged on Aug. 15, 1956, at 11 months of age on a regular diet for age with added sodium chloride and sodium citrate to supply a daily total of 165 mEq. of sodium.

Second Hospital Admission.—He was readmitted to the hospital on Aug. 31, 1956, two weeks after discharge, because of vomiting. Examination at this time revealed a good state of hydration. The eczematoid rash was unchanged, and fecal masses again were palpable. He was placed on a normal diet for age to which 5 gm. of salt was added daily. Doses of 90 mg. of thyroid, U. S. P. were continued. His appetite was good, and he was able to maintain hydration and serum electrolytes in the normal range. Two months after admission,

TABLE 4.—*Bone Maturation*
(Greulich and Pyle)

Chronologic Age, Mo.	Bone Age (Wrist), Mo.
7	0
12	3
16	6
19	9
22	18
30	30

the supplemental salt was reduced to 2 gm. daily without untoward effect. Four months after admission extra salt was completely eliminated from the diet, but he continued to maintain hydration and weight. This was attributed to a good appetite and increased intake of food. Numerous studies were undertaken during this hospital stay to define the defect responsible for sodium wasting. These will be described in detail (*vide infra*). At 14 months of age the developmental quotient (Gesell) was 87. During this period of hospitalization intercurrent respiratory infection occurred occasionally, and a generalized pustular eruption due to hemolytic Micrococcus pyogenes supervened on three occasions. All infections responded favorably to appropriate antimicrobial therapy.

Third Hospital Admission.—He was readmitted to the hospital electively for study on August 5, 1957, at age 23 months. In the interim, his progress had been satisfactory. He had continued to eat well, gain weight and improve developmentally. Despite this progress, however, his somatic growth remained below normal for age (Fig. 2). He was active, happy, and ran about the ward as a normal child.

Special Laboratory Investigation

Material and Methods.—Studies to elucidate the cause of salt losing were performed over a period of 16 months. Dietary intake was uniform for seven days or more prior to each study period. All feedings were prepared from the same batch

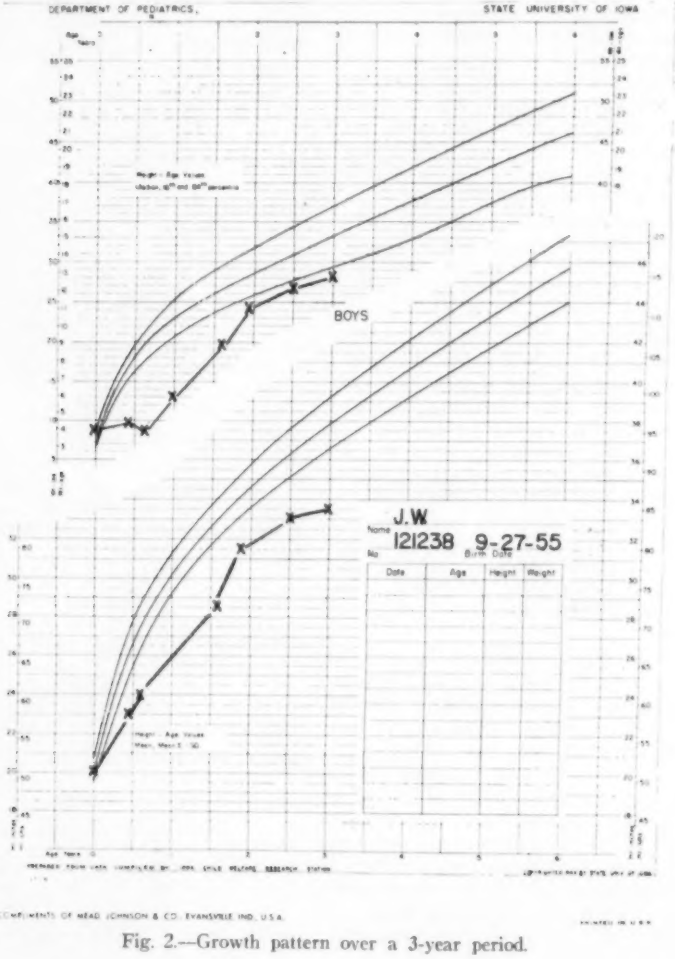

Fig. 2.—Growth pattern over a 3-year period.

of canned foods under the supervision of the dietary department. Random sampling revealed uniform electrolyte composition for each batch analyzed. All food refused at each meal was weighed, permitting estimation of the quantity of electrolyte ingested. Variation in sodium intake was achieved by adding known amounts of salt to milk or by changing to a low-sodium diet of known content.

Twenty-four hour collections of urine were preserved by refrigeration. Sodium and potassium were measured by flame photometry, chlorides by the method of Schales,[16] urinary 17-ketosteroids by the method of Sobel,[16] and urinary ketogenic steroids by the method of Norymberski.[17] Urinary aldosterone was measured by Lieberman and Leutscher and serum 17-hydroxycorticosteroids by the method of Nelson and Samuels.[18]

Result and Interpretation

The initial hospitalization at age 7½ months lasted three and a half months and permitted documentation of the clinical aspects of the disease. It was demonstrated that adrenal and renal functions were normal, and that salt depletion was refractory to corticotropin, desoxycorticosterone acetate and prednisone (Δ-1-cortisone) in therapeutic doses. Improvement occurred only when large loads of salt were given. The second and third hospitalizations at 11½ and 23 months of age and lasting nine and two months respectively permitted definition of the renal origin of salt wasting and the unresponsiveness of the renal tubule to endogenous aldosterone and exogenous mineralocorticoids.

A. Adrenal.—Assessment of adrenal function revealed no significant abnormality. The ability of the kidney to produce a diuresis in response to a water load is impaired with adrenal insufficiency. This has been employed as a test of adrenal function.[19] A modification of this test was found to be normal on two occasions.[20] More than 90% of the water administered was excreted in two hours.

Normal values for circulating 17-hydroxycorticosteroids in children have been established by Ely et al.,[21,22] who found mean levels of 12μg/100 cc. and a range of 0 to 28.7μg/100 cc. The value of 24μg/100 cc. would place this patient's serum 17-hydroxycorticosteroids in the high normal range. Basal eosinophil counts were always high (700-1,500 per cubic millimeter).

The responsiveness of the adrenal to corticotropin has been used as a test of its functional capacity.[21,23-26] Twenty-four units of corticotropin gel were administered intramuscularly daily for four days. The eosinophil count of 1,474 per cubic millimeter immediately prior to corticotropin administration dropped below 22 per cubic millimeter and remained in this range until completion of the test, after which it rose to original levels. Under corticotropin stimulation, the circulating 17-hydroxycorticosteroids rose from 24μg/100 cc. to 120μg/100 cc. The excretion of urinary 17-ketosteroids and ketogenic steroids, 0.5μg/day and 1.5μg/day respectively at the start of the test period, rose to 2.2μg/day and 25.3μg/day in four days (Table 2). These responses were considered evidence for adequate adrenal function.

Aldosterone was present in the urine. Normal values have been reported by Lieberman and Leutscher as 2μg.-3μg/day on a standard diet.[27] A five- to tenfold rise is expected with sodium restriction.[27] This child excreted 335μg/day on a standard hospital diet for age (35-40 mEq. Na) while in apparent chemical balance. Addition of 85 mEq. sodium as salt to the diet for several days reduced the urinary excretion of aldosterone to 2.5μg/day. Salt restriction, on the other hand, caused a rise in urinary aldosterone to 887μg/day (Figs. 3 and 4).

B. Thyroid.—The patient had many clinical stigmata of hypothyroidism, including retarded somatic development, retarded skeletal maturation, and constipation. The initial elevation of protein-bound iodine undoubtedly reflected the prolonged use of iodochlorhydroxyquin cream prior to hospitalization. The decline of the protein-bound iodine after the medication was discontinued supported this contention. The initial I^{131} uptake was low, but a threefold rise occurred after TSH stimulation. These findings were compatible with hypothyroidism secondary to hypopituitarism. Accord-

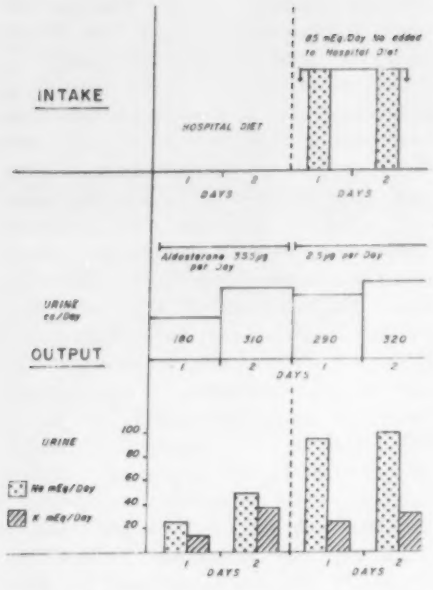

Fig. 3.—Urine volume, urine sodium and aldosterone excretion on standard hospital diet, and with addition of 85 mEq. sodium per day.

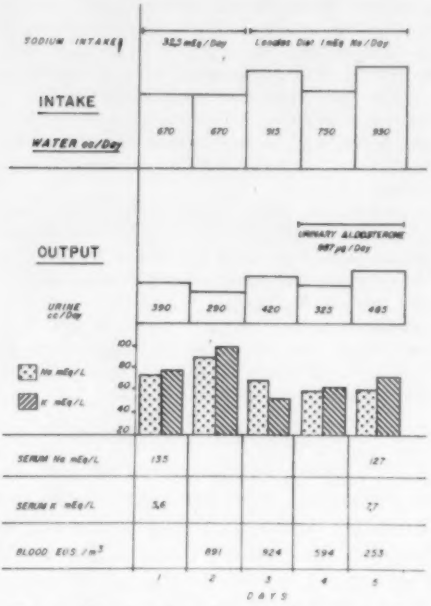

Fig. 4.—Changes in urinary and serum sodium and potassium concentrations with reduction of sodium intake.

ingly, treatment with increasing doses of thyroid was prescribed.

Subsequent events revealed this child to be euthyroid. It is probable that the effects on tests of thyroid function were due to iodochlorhydroxyquin cream, although it is possible that persistent dehydration and general debilitation caused a temporary state of pituary insufficiency. Response to exogenous desiccated thyroid could not be evaluated, inasmuch as marked general improvement followed the addition of large loads of salt to his diet, masking any effect which might have been attributed to thyroid.

Bone age at 7 months was that of a newborn, but skeletal maturation approached the chronologic age at 30 months. When it became evident that the child was euthyroid at 2 years of age, exogenous thyroid was discontinued. Skeletal maturation continued at a normal rate, however.

C. Renal.—The renal function studies are summarized in Table 5. Routine urinalyses were consistently normal. Intravenous pyelography revealed no structural abnormality. The ability to concentrate and dilute urine was not impaired. Specific gravity ranged from 1.013 to 1.035. With water loading the specific gravity fell to 1.004, and it rose to 1.035 when water was restricted for six

TABLE 5.—*Renal Function Tests*

Glomerular	Results
NPN (mg. %)	25-31 (range)
BUN (mg. %)	11
Endogenous creatinine clearance	115 cc/min/1.73 sq. m.
Tubular	
pH	4.5-8 (Avg. 5.7)
Titratable acidity, mEq/day	2.3-12.6
Specific gravity	1.004-1.038 (usual 1.019-1.026)
Water loading	90% load excreted in 2 hr.
Ammonia, mEq/sq. m/day	15-40
Acetazolamide response	Normal
Phosphorus reabsorption	86%
Amino acids, mg/lb/day	1-1.1
Glucose	No determinable losses
Organic acids, mEq/kg/day	0.7-1.2
Combined	
PSP	80% excreted in 2 hr.
IVP	Normal
Routine urinalyses	Always normal

hours or more. Several determinations of NPN and BUN throughout the period of evaluation never exceeded normal. Endogenous creatinine clearance was 115 cc/min/1.73 sq. m.

The ability of the kidney to acidify urine, to secrete ammonia, and to respond to carbonic acid anhydrase inhibitor and NH_4Cl loading was not impaired. The administration of acetozolamide resulted in a decline in urinary titratable acidity from 12.6 to 2.3 mEq/day with corresponding rise in urinary pH from 5.75 to 7.25. This was accompanied by a small rise in sodium and potassium excretion.

Titratable acidity ranged between 19-27 mEq/sq. m/day, on a standard diet, rising to 37 mEq/sq. m/day in association with the acidosis induced by NH_4Cl loading (normal 5-20 mEq/sq. m/day).[28,29]

Urinary ammonia excretion measured 15-40 mEq/sq. m/day during a control period and increased to 79 mEq/sq. m/day when NH_4Cl, 6 gm/sq. m/day was prescribed for four days (normal 20-30 mEq/sq. m/day, rising to 70-150 mEq/sq. m/day with acidosis).[29,30]

Tubular reabsorption of phosphorus[31] was 86%. Daily urinary excretion of organic acids on standard diet ranged from 0.7-1.2 mEq/kg/day (normal 1 mEq/kg/day).[29] Excretion of amino acids ranged from 1-1.1 mg/lb/day (normal less than 2 mg/lb/day).[32]

1. Effects of Salt Intake: The urinary response to salt loading and restriction are depicted in Figures 3, 4, and 5. The renal excretion of salt fluctuated as salt was added or removed from the diet.

With an intake approximating 35 mEq/day the daily excretion of sodium ranged between 26-32 mEq/day. Further, urinary sodium rose to 70-100 mEq/day when the daily diet contained 90-110 mEq. sodium (Fig. 5). Salt restriction by the substitution of a sodium-free powdered milk preparation (Lonalac) for the standard diet produced dramatic clinical and chemical changes (Fig. 4). By the third day, weight loss, dehydration, pallor, and imminent col-

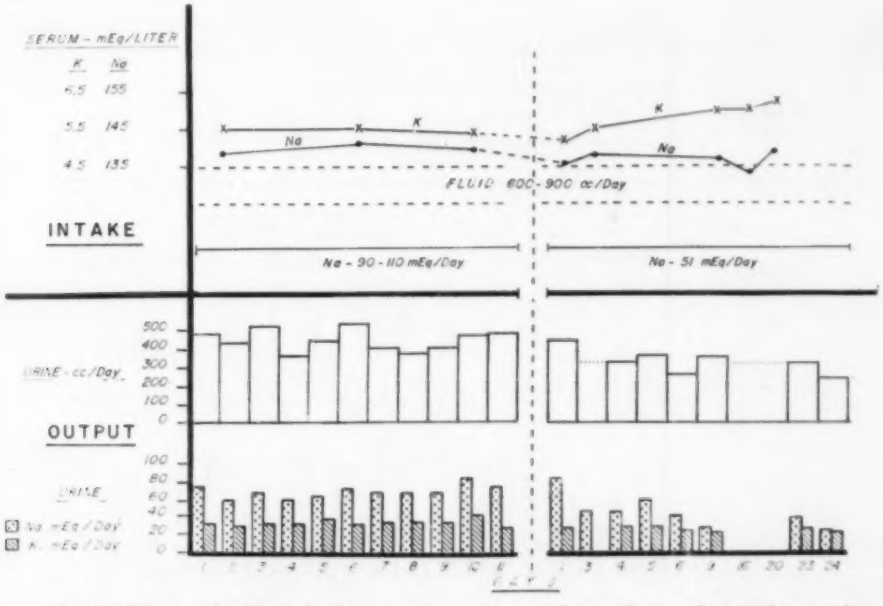

Fig. 5.—Effects of sodium intake on urine volume, urine sodium and potassium, and serum sodium and potassium.

lapse were evident. The serum sodium declined from 135 to 127 mEq/L. and the serum potassium rose from 5.6 to 7.7 mEq/L. The daily sodium excretion (26-29 mEq/day or 74-90 mEq/L. during the control period) remained essentially unchanged. Despite a strong stimulus for sodium conservation, the infant was unable to reduce the urinary concentration of salt significantly. The minimum concentration achieved was 59 mEq/L. (Fig. 4). The effect on total daily excretion of salt was small. On the second day of salt deprivation, sodium excretion declined to 19 mEq/day from control values of 26-29 mEq/day. However, sodium excretion rose again to 29 mEq/day on the third day of salt restriction. The drop on the second day reflected a decrease in urinary output for that day.

2. Effects of Corticotropin and Mineralocorticoids: The response of the adrenals to stimulation by corticotropin has already been mentioned. Corticotropin produced a rise in circulating 17-hydroxycorticosteroids, urinary ketogenic steroids, and a fall in circulating eosinophils (Table 2). A course of corticotropin gel 10 units intramuscularly daily and later raised to 15 units while on standard diet with 5 gm. of salt added produced a steady rise in sodium excretion rather than a fall (Fig. 6).[33] When corticotropin was discontinued, the urinary excretion of sodium returned to pretreatment levels. Desoxycorticosterone acetate had no significant effect on the excretion of salt or potassium (Fig. 7). After a three-day control period of constant salt intake, desoxycorticosterone acetate 3 mg/day was administered intramuscularly for three days. The urinary excretion of sodium and potassium remained essentially unchanged throughout this period.

Single doses of fludrocortisone (9α-fluorohydrocortisone) and 2-methyl-9α-fluorohydrocortisone given intravenously and orally (Figs. 7 and 8) were also without effect. Control studies and the experience of others would lead one to expect a significant fall in sodium excretion, and a variable effect on potassium excretion (Fig. 8).[34]

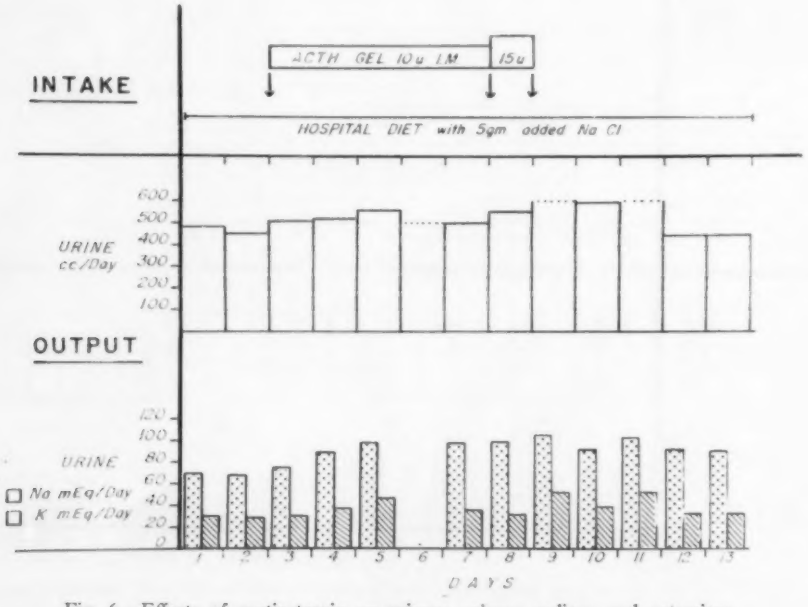

Fig. 6.—Effects of corticotropin on urinary volume, sodium, and potassium.

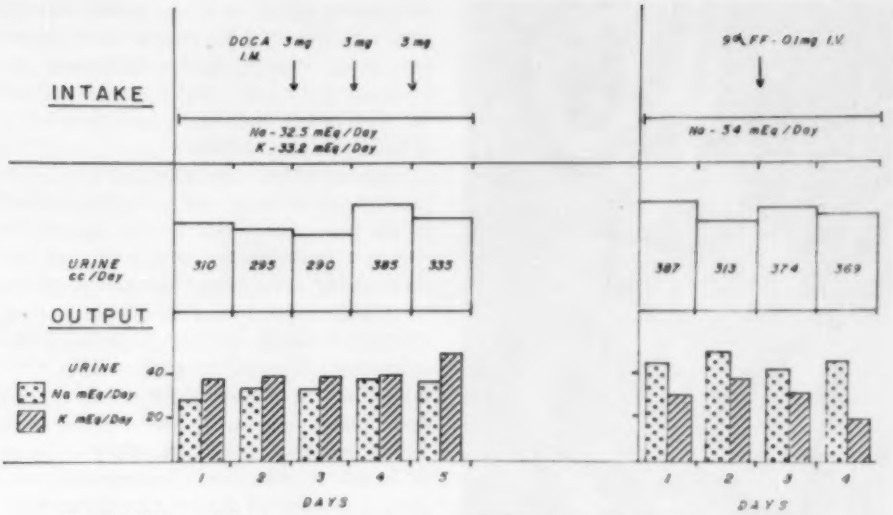

Fig. 7.—Effects of desoxycorticosterone acetate (DOCA) and (9α-fluorohydrocortisone) on urinary sodium and potassium excretion.

Summary of Findings

These studies revealed no evidence of adrenal or renal dysfunction other than tubular insensitivity to mineralocorticoids. Aldosterone was present in the urine and responded in the expected fashion to salt loading and restriction.[35-39] The high urinary aldosterone values on a standard diet may have reflected attempts at maximum sodium conservation. The serum potassium was not elevated at that time, and the immediate stimulus for increased aldosterone production may have been a decrease in extracellular volume.

A defect in renal salt conservation was conclusively demonstrated. Despite severe

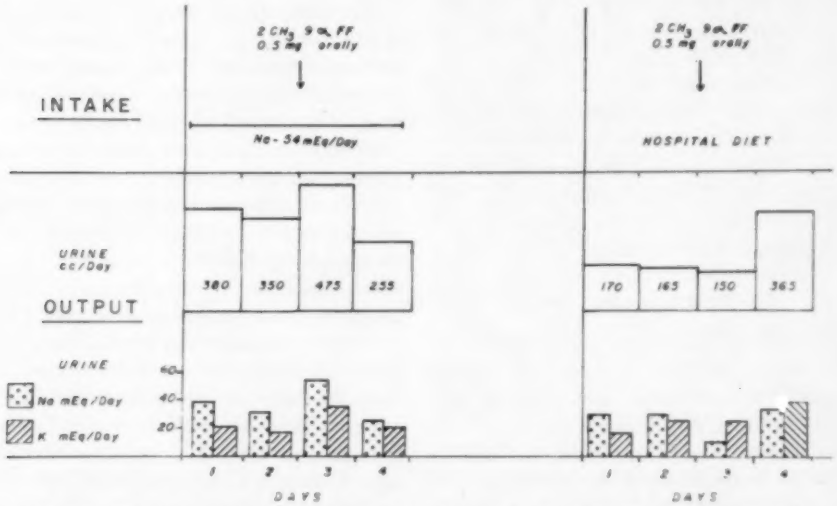

Fig. 8.—Effects of 2-methyl-9α-fluorohydrocortisone (2 $CH_2$9αFF) on urinary excretion of sodium and potassium. Patient on left, control on right.

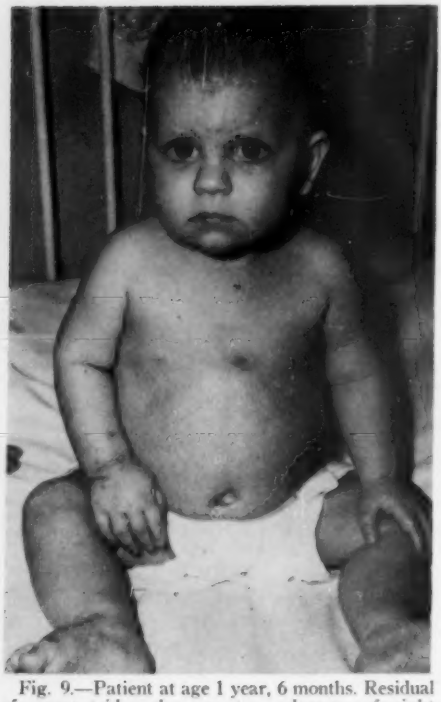

Fig. 9.—Patient at age 1 year, 6 months. Residual of eczematoid rash present on dorsum of right wrist.

clinical and laboratory evidence of salt depletion, the urinary concentration of sodium did not fall below 59 mEq/L. At this time urinary aldosterone levels were extremely high (887 μg/day). One must conclude that the renal tubules are refractory to aldosterone. The inability of the tubules to respond to other potent mineralocorticoids such as desoxycorticosterone acetate, fludrocortisone, and 2-methyl-9α-fluorohydrocortisone by a reduction in salt excretion further strengthened this hypothesis.

Comment

Regulation of salt and water balance depends on the integrity of the central nervous system,[40] the endocrine and exocrine systems,[41] and on the intact kidney. No abnormality of the central nervous system could be demonstrated in the present patient. No clinical evidence of neurologic disease was detected. X-rays of the skull and the electroencephalogram were normal. He was somewhat retarded in mental development, but steady improvement accompanied appropriate treatment. At 2½ years of age he was active and alert, and motor coordination was excellent.

The role of the adrenal gland in regulating the excretion of sodium and potassium in the urine and sweat is well known.[10,11] Adrenalectomy results in loss of salt and retention of potassium. The administration of adrenal cortical hormones reverses these effects.[42] Certain clinical features of this case such as failure to thrive, chronic dehydration, hyponatremia, hyperkalemia, and eosinophilia suggested adrenal insufficiency.

The retarded bone age, normal serum 17-hydroxycorticosteroid concentrations and normal urinary 17-ketosteroid excretion excluded the salt-losing form of congenital adrenal hyperplasia.

Primary adrenal insufficiency was excluded by the normal circulating 17-hydroxycorticosteroid concentration and by the magnitude of response to test doses of corticotropin. Partial adrenal insufficiency has been described in association with normal 17-hydroxycorticosteroid levels, but the response to corticotropin is curtailed in such patients.[43]

The presence of large amounts of aldosterone in the urine, and the response of urinary aldosterone to salt loading and depletion strengthened the impression of normally functioning adrenal glands.

Hypopituitarism was suggested by poor growth, apparent secondary hypothyroidism, and suspected adrenal insufficiency. Pituitary insufficiency as a cause of adrenal failure in infants is difficult to establish. It has been documented with frequency only in anencephalic monsters and is rare in the absence of demonstrable cranial defects.[44-47] Early death is the rule in such cases, and normal circulating 17-hydroxycorticosteroid concentrations would be unexpected. Hypoglycemia has been described in children who later develop gonadal insufficiency attributed to pituitary insufficiency, but frank Addisonian crises have not been encountered.[48]

No abnormality in carbohydrate metabolism was demonstrated in the present case. Fasting blood sugar and glucose tolerance tests were normal.

A number of clinical and laboratory observations suggested secondary hypothyroidism. The initially low I^{131} uptake and its marked increase in response to thyroid-stimulating hormone are consistent either with secondary hypothyroidism or with the effects of exogenous iodides. The effect of iodochlorhydroxyquin cream on the pituitary-thyroid axis has not been reported. Turner [49,50] reported reduced 24-hour radioactive iodine uptake in patients who developed goiter from exogenous iodides. Levy et al.[51] found that the blocking effect of exogenous iodides could not be overcome by the administration of thyroid-stimulating hormone (TSH). Newman and Cupp,[52] on the other hand, found that the suppressing effects of iodinated compounds on I^{131} uptake could be overcome with thyroid-stimulating hormone, if such compounds had been given only for short periods.

These data are difficult to interpret. The complete recovery of thyroid function establishes the temporary nature of the difficulty. It is possible, of course, that the extremely debilitated condition of the patient produced a temporary state of pituitary insufficiency.[48]

Recent reports [53] postulate increased antidiuretic hormone secretion as a cause of hyponatremia. The syndrome has been described in association with several unrelated conditions, including pulmonary tuberculosis,[54,55] bronchogenic carcinoma,[53,55] a variety of disorders of the central nervous system,[56-59] and in the postoperative state.[60,61] It is suggested that excessive secretion of antidiuretic hormone suppresses production of aldosterone by causing retention of water and expansion of extracellular volume. Reduced secretion of aldosterone, in turn, results in loss of salt by way of the kidney. The cause of excessive production of antidiuretic hormone is not known. Many such patients exhibit no symptoms and some respond to restriction of water with or without an increase in salt intake.[58] In contrast, our patient demonstrated overt dehydration in association with his hyponatremia. He tolerated water loads well and required both water and salt for repletion.

Salt loss may occur in association with specific renal disease or secondary to defects in renal tubular transport mechanisms. In the former, severe renal insufficiency is present.[62-66] In the latter, cation wastage is due to failure of the urine to acidify, and the need for positive ions to accompany negative ions.[67-69] Renal function in our patient was unimpaired. The ability to concentrate and dilute urine, to acidify urine, and to produce ammonia was normal. Excessive renal excretion of glucose, amino acids, and phosphorus could not be demonstrated.

The mechanism for sodium conservation in the intact kidney is usually extremely efficient. When necessary, urine with a sodium concentration of 1 mEq/L. or less can be produced.[70,72] This is essential for maintaining constant serum osmolarity. The ability to conserve sodium in this patient was impaired. Despite the stimulus of sodium deprivation, urinary concentration of sodium less than 59 mEq/L. could not be achieved, even though large amounts of aldosterone were found in the urine. These findings indicate unresponsiveness of the renal tubule to aldosterone. Failure of the mineralocorticoids, desoxycortiscoterone acetate, fludrocortisone, and 2-methyl-9α-fluorohydrocortisone to augment the conservation of sodium further strengthened the hypothesis. The renal tubule refractory to aldosterone is analogous to absence of the steroid in terms of this function. To this extent, the clinical picture resembled Addison's disease.

The cause of the defect is unknown. A genetic etiology seems unlikely from the negative family history but it cannot be excluded. Recent studies have demonstrated transient differences in the activity of various enzymes in the newborn.[73] It seems possible that something environmental might affect the development of the enzyme trans-

port systems necessary for sodium reabsorption.

The rarity of this condition is indicated by the paucity of reported examples. Payne [74] mentions the existence of tubular salt wasting refractory to desoxycorticosterone acetate in infants during the first few weeks of life in association with abdominal surgery or infections producing electrolyte disturbances. The disorder is self-limited, and spontaneous recovery takes place in a few weeks.

Cheek and Perry [14] describe a 3-month-old infant with failure to thrive and chronic renal salt wasting. The patient failed to respond to desoxycorticosterone acetate but improved when given large salt loads. This infant had no demonstrable renal or adrenal defect. Direct measurements of aldosterone output were not made. Low sweat electrolytes were taken on evidence of adequate mineralocorticoid production. Spontaneous improvement occurred over a five-month period.

The prognosis of the tubular lesion is speculative because of limited experience, but the patient of Cheek and Perry [14] improved. Clinical improvement followed correction of deficiencies in the present case over a period of several months. The defect could still be demonstrated under stress at the age of 2 years, but chemical equilibrium could be maintained on a standard diet. The parents indicate that growth and development are steady, though still somewhat behind normal at 3 years of age. He has not experienced severe stress at home, but minor infections, including otitis media, have been well tolerated. This experience suggests gradual adaptation, either by return of normal function or by development of an alternate metabolic pathway.

The present patient has provided an opportunity to study certain aspects of the mechanism for the excretion of electrolytes by the kidney. An interrelationship between the excretion of sodium and that of potassium has been recognized on numerous occasions.[75-84] The inability of this patient to reduce the concentration of sodium in the urine beyond 59 mEq/L. despite salt deprivation and steroid administration made it possible to observe some of the relationships between sodium and potassium at the renal level. Present data seem to support the hypothesis that tubular exchange of potassium for sodium is the source of urinary potassium. Urinary potassium is essentially the result of distal secretion following complete reabsorption of potassium by the proximal tubule. Certain recent observations are less conclusive, but many studies provide a firm basis in support of this concept.[85,86] The exchange of potassium for sodium may be influenced by steroids,[87] by various diuretic agents,[88] and by the integrity of the carbonic anhydrase system.[89] It has been shown clearly that a defect in the tubular reabsorption of sodium existed in this patient and that with salt depletion conservation of filtered sodium was incomplete and fixed at about 60 mEq/L. Continued salt restriction had no effect in reducing the urinary concentration of sodium, resulting in continued loss of this cation. The fall in urinary potassium accompanying salt deprivation was followed by a clear rise in serum potassium (Fig. 5). Sufficient sodium would have been available in the tubular urine for exchange in a normal person, but restricted reabsorption of tubular sodium in this child limited potassium excretion. Potassium was retained accordingly and a rise in serum value was observed. Furthermore, since sodium depletion regularly stimulates aldosterone secretion, it might be expected to cause loss of potassium, inasmuch as steroids accelerate the exchange of potassium for sodium.[90,91]

As the sodium intake in this patient was increased and the sodium excretion exceeded the minimal level, potassium excretion increased and the serum potassium fell to normal. Although the effects observed were not large, the changes in urinary and serum potassium were clearly related to the sodium excretion. The role of redistribution of potassium in various fluid compartments in regulating the serum potassium changes

noted with sodium loading and depletion cannot be defined with present data.

The possible existence of a salt-losing steroid responsible for the salt loss cannot be excluded with any certainty. The occurrence of such a substance in newborns has been suggested by Klein et al.[22]

Summary

An infant is described with chronic dehydration, hyperkalemia, hyponatremia, and marked somatic retardation suggesting adrenal insufficiency. Paradoxically, the circulatory 17-hydroxycorticosteroids were normal, and stimulation with corticotropin caused a normal response.

Subsequent studies revealed that a salt-losing renal tubular defect was responsible for the symptoms and that the defect was manifested by a renal refractoriness to aldosterone. The hypothesis (of renal tubular insenitivity to mineralocorticoids) was further strengthened by the demonstration of the inability to induce sodium conservation by the administration of desoxycorticosterone acetate, fludrocortisone, and 2-methyl-9α-fluorohydrocortisone.

Initially, large loads of salt were required to correct the serum electrolytes. Subsequently, the child was able to maintain electrolyte balance on standard diet, but could not tolerate salt deprivation.

Drs. A. H. Lieberman and J. A. Leutscher made the aldosterone determinations, and Dr. R. S. Ely the 17-OHCS determinations. Dr. H. C. Peltier and Dr. C. J. O'Donovan, of the Upjohn Company, Kalamazoo, Mich., supplied the steroids used in this study, and Dr. H. A. Joos helped in the preparation of this manuscript.

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Poliomyelitis Under One Year of Age

Clinical and Laboratory Findings in a Group of 529 Patients with Poliomyelitis Younger than One Year of Age

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The number of reports in the world medical literature on the clinical and laboratory findings in poliomyelitis have been accumulating rapidly ever since the description of the disease nearly a century ago. However the number of such reports dealing exclusively with infants is relatively small, and most reports deal with rather small numbers of cases.

The authors believe that the present report should be of interest, dealing, as it does, with 529 cases of poliomyelitis in infants under one year of age, treated at Rambam Government Hospital and observed by the same persons.

Material and Methods

The 529 cases of poliomyelitis which serve as the basis of the present report were treated in the Pediatric Department B of this hospital from the end of 1949, when an epidemic outbreak of poliomyelitis in Israel first became apparent, to the end of 1956.

During this period 1,527 cases of poliomyelitis in all age groups were hospitalized. The group of infants younger than one year of age represented 28% to 43% of the total number of patients in different years (Table 1).

With the exception of a negligible number of patients, all the paralytic cases of poliomyelitis in this age group reached the hospital a day or two after the appearance of gross muscular weakness. The group of patients with nonparalytic poliomyelitis reached the hospital, in the majority, with the general diagnosis of meningitis or meningeal irritation. Several cases were sent with the proper diagnosis by physicians serving small communities where poliomyelitis was widespread. Whereas no efforts were spared in this hospital to limit the group with nonparalytic poliomyelitis to cases definitely diagnosed as such, certain omissions must have occurred, both ways, as adequate virological laboratory facilities were available only during the last two years of the seven-year period of the epidemic. The diagnosis of nonparalytic poliomyelitis was based on the clinical picture, on epidemiological data, and on the absence of positive complement-fixation tests for all the commoner viruses known to cause abacterial meningitis, on negative agglutination tests for leptospirosis, and a low level of diastase in the blood. The diastase level is higher than normal in patients with leptomeningitis associated with mumps.

All patients diagnosed on admittance as having poliomyelitis underwent the following examinations: complete blood count, urine and stool examinations, examination of the cerebrospinal fluid for white blood cells and protein content. Stool and blood specimens were sent to the Virus Laboratory of the Hebrew University-Hadassah Medical School. The patient's temperature was recorded three times daily. Paralyzed limbs were given orthopedic care in order to prevent contractures. In cases with peripheral and/or central respiratory paralysis the iron lung was used, and in several patients a tracheotomy was performed in order to

TABLE 1.—*Yearly Distribution of Cases of Poliomyelitis Younger than One Year of Age*

Yr.	Total No. (All Ages)	Cases Under 1 Yr. of Age	
		No.	%
1950	414	149	36
1951	245	91	36
1952	226	73	33
1953	162	70	43
1954	215	73	34
1955	163	44	27
1956	102	30	29
Total	1,527	529	35

Submitted for publication Nov. 16, 1958.

Pediatric Department B, Rambam Government Hospital, Haifa.

This study was suported by a grant from the van Leer Foundation.

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permit better drainage of bronchial secretions.

After the fall of temperature to normal, a second examination of the protein content of the cerebrospinal fluid was performed and the number of white blood cells per cubic millimeter of fluid was determined. The average period of hospitalization was 21 days. Special cases remained for longer periods of time because of persistent need of artificial respiration, or, in the most severely affected, because of social considerations.

The performing of a lumbar puncture was frequently accompanied with technical difficulties resulting in "dry" or "bloody" tap. This factor, coupled with inability to perform a lumbar puncture in babies in very bad condition on admission, caused a reduction of the number of the initial examinations of the cerebrospinal fluid, as compared with the number of patients. A further discrepancy was caused by sometimes obtaining a too small quantity of cerebrospinal fluid to permit a full examination. In such case one of two examinations was performed. Thus in a total of 450 patients the protein content of the cerebrospinal fluid was examined and in 455 patients the number of white blood cells per cubic millimeter of fluid was established (Table 2).

The second lumbar puncture was performed on the 14th-18th day of illness, several days after the fall of temperature to normal. A further reduction of the number of cerebrospinal fluid examinations performed was caused by patients that died later in the hospital. Thus in a total of 312 cases the protein and the number of white blood cells in the cerebrospinal fluid were determined after the second week of illness. The identical number of examinations is incidental and does not mean necessarily that both examinations were performed on the same patient's cerebrospinal fluid.

TABLE 2.—*Number of Cerebrospinal Fluid Examinations Performed in a Group of 529 Patients with Poliomyelitis Younger than One Year of Age*

Clinical Type of Poliomyelitis	No. of Cases	No. of CSF Examinations on Admission		No. of CSF Examinations After Fall of Temp.	
		WBC *	Protein †	WBC *	Protein †
Nonparalytic	56	53	50	44	43
Spinal	350	312	313	229	231
Bulbar	11	6	5	0	0
Encephalitic	2	1	1	0	0
Spinal-bulbar	57	38	36	8	8
Spinal-encephalitic	5	3	4	3	3
Bulbar-encephalitic	—	—	—	—	—
Spinal-facial	22	20	19	16	16
Facial	15	14	14	9	9
Spinal-bulbar-encephalitic	7	4	4	1	1
Spinal-facial-encephalitic	4	4	4	2	1
Total	529	455	450	312	312

* WBC=number of white blood cells per cubic millimeter of cerebrospinal fluid.

† Protein=milligrams of protein per 100 ml. of cerebrospinal fluid.

The number of white blood cells in the cerebrospinal fluid ranged from 7 to more than 900 per cubic millimeter. The cases were classified in five groups according to the number of white blood cells as follows: (*a*) normal—when the number of white blood cells per cubic millimeter of cerebrospinal fluid was less than 10; (*b*) slightly elevated—when the number of white blood cells per cubic millimeter was between 11 and 30; (*c*) moderately elevated—when the number of white blood cells per cubic millimeter was between 31 and 70; (*d*) markedly elevated—when the number of white blood cells per cubic millimeter of cerebrospinal fluid was between 71 and 150, and (*e*) very markedly elevated—when the number of white blood cells per cubic millimeter was greater than 150.

The protein content of the cerebrospinal fluid ranged from less than 30 mg. per 100 ml. of cerebrospinal fluid to 90 mg. per 100 ml. The cases were classified in five groups according to the quantity of protein in the cerebrospinal fluid as follows: (*a*) cases with normal protein content, when it was less than 30 mg. per 100 ml. of cerebrospinal fluid; (*b*) cases with slightly elevated protein content, when it was between 31 and 40 mg. per 100 ml. of cerebrospinal fluid; (*c*) cases with moderately elevated protein content, when it was between 41 and 60 mg. per 100 ml. of cerebrospinal fluid; (*d*) cases with markedly elevated protein content, when it was between 61 and 80 mg. per 100 ml. of cerebrospinal fluid, and (*e*) cases with very markedly elevated protein content, when it was more than 80 mg. per 100 ml. of cerebrospinal fluid.

When examination of the number of white blood cells or of the protein content was performed on admission and after the fall of temperature to normal, a comparison was made between the two results. An increase or a decrease in the second examination was defined as a change of the initial examination value corresponding to a difference between at least two of the above-mentioned groups.

The clinical types of poliomyelitis were defined as follows: (*a*) nonparalytic type, when diagnosis of poliomyelitis was made in a case without evident muscle weakness or signs of cranial nerve involvement, according to the criteria outlined above; (*b*) spinal type, when the patient presented weakness of muscles of limbs and trunk only; (*c*) bulbar type, when signs of involvement of nuclei situated in the medulla only were present; (*d*) en-

TABLE 3.—*Distribution of Cases of Poliomyelitis Younger than One Year of Age According to Age in Months*

Yr.	Age in Months												
	1	2	3	4	5	6	7	8	9	10	11	12	Total
1950	1	2	4	9	18	18	12	14	13	15	11	31	148
1951	1	6	6	5	4	5	5	10	14	8	10	17	91
1952	—	1	1	4	1	8	15	8	10	8	6	11	73
1953	—	—	2	3	6	1	11	7	16	4	7	13	70
1954	—	—	—	4	3	7	6	11	13	10	6	13	73
1955	—	—	1	1	4	5	4	5	10	3	5	6	44
1956	—	—	—	—	1	1	4	8	3	8	2	3	30
Total	2	9	14	26	37	45	57	63	79	56	47	94	529

cephalitic type, presented by general confusedness, unconsciousness, generalized convulsions, anisocoria, and other minor signs of encephalopathy, and (*c*) facial type, when only weakness of face muscles innervated by the facial nerve were present. The combination of signs of these five types were classified as follows: spinal-bulbar type; spinal-encephalitic type; bulbar-encephalitic type; spinal-facial type; spinal-bulbar-encephalitic type; and spinal-facial-encephalitic type.

Age Distribution

The age distribution of this group of patients is presented in Table 3. There were 25 cases (4.7% of the total number of patients) less than 3 months old; 108 cases (20.4%) were between 3 and 6 months old, and 396 (74.9%) were older than 6 months.

All but five of the cases less than 3 months old appeared during the first two years of the epidemic. The distribution of the 4 to 6 month and 7 to 12 month age groups was similar throughout the years.

The appearance of 80% of the cases of poliomyelitis in the 0-3 month age group during the first two years after the epidemic outbreak (1950-1951) was evidently related to the mass exposure of babies during these first years of Isreal's independence. The mass immigration during these years brought a marked lowering of hygenic and living standards of the population. Later on, with permanent settlement of immigrants in cities and agricultural settlements, exposure to the poliomyelitis virus of very small babies was reduced.[1]

Clinical Types of Poliomyelitis

The number of patients in each clinical type group is presented in Table 4. Of all the cases 65% had spinal type paralyses; 10.5% had spinal-bulbar type, and the same

TABLE 4.—*Distribution of Cases of Poliomyelitis Under One Year of Age by Clinical Type and Age Groups*

Clinical Type of Poliomyelitis	Age in Months												
	1	2	3	4	5	6	7	8	9	10	11	12	Totals
Nonparalytic	—	—	3	6	6	8	6	7	4	6	3	7	56
Spinal	2	6	5	14	22	23	36	43	57	39	35	68	350
Bulbar	—	1	1	—	1	3	1	—	2	—	1	1	11
Encephalitic	—	—	—	—	2	—	—	—	—	—	—	—	2
Spinal-bulbar	—	2	1	4	3	6	10	6	4	7	5	9	57
Spinal-encephalitic	—	—	1	1	—	2	—	1	—	—	—	—	5
Bulbar-encephalitic	—	—	—	—	—	—	—	—	—	—	—	—	—
Spinal-facial	—	—	1	1	1	—	1	4	5	2	2	3	22
Facial	—	—	—	—	1	1	2	2	3	2	—	4	15
Spinal-bulbar-encephalitic	—	—	1	—	—	1	1	—	3	—	1	—	7
Spinal-facial-encephalitic	—	—	1	—	1	1	—	1	—	—	—	—	4
Totals	2	9	14	26	37	45	57	64	78	56	47	94	529

proportion of the group had no apparent paralyses (nonparalytic group).

The age distribution of the cases within each clinical type group is illustrated in Table 4. There were no significant differences in the age distribution in each clinical type group as compared with the distribution of the whole group.

These patients represented 34.6% of the total number of patients hospitalized with poliomyelitis throughout the same seven-year period at Rambam Government Hospital. The number of patients in the different clinical type groups represented a similar portion of the respective number of patients of all ages, with the notable exception of the bulbar, encephalitic, and bulbar-encephalitic patients: only 11% of all the bulbar cases were younger than one year; 15% of the encephalitic group were younger than a year, and no bulbar-encephalitic cases were less than 12 months of age. The possibility that some of the severer cases of encephalopathy observed in the Department as part of the clinical picture of severe toxicosis and other metabolic disorders could have been poliomyelitis cases must be considered retrospectively.

Appearance of Muscular Weakness

The day of illness when muscular weakness was observed for the first time is presented in Table 5. In 36 (7%) of the 473 cases with paralytic poliomyelitis the day of appearance of muscle weakness was not definitely known. In 51% (225 cases) it appeared during the first three days of illness; in 35% (154 cases) muscle weakness was first apparent between the fourth and sixth days of illness, and in 11% (48 cases) the paralyses were observed after the sixth day. In 2% (10 cases) it was reported to have appeared after the 10th day of acute illness.

The appearance of muscular weakness, signs of bulbar or cranical nerve involvement, or encephalopathy during the first three days of illness was twice as frequent among patients with facial, encephalitic, or bulbar type of poliomyelitis as among patients with spinal nerve involvement. Whereas this may be a consequence of higher vulnerability of cerebellar and medullar nerve tissue during this period of life, it must be borne in mind that signs of involvement of these centers are much more noticeable than weakness of a limb or body muscle in an infant.

Signs of Meningeal Irritation

Four signs were considered to be caused by meningeal irritation at the early stage of the disease: neck rigidity, a positive Kernig's sign, a positive Brudzinski's sign, and a bulging anterior fontanel. The presence of a positive Kernig's sign, a bulging fontanel, or neck rigidity, alone or together, was considered to indicate meningeal irritation. The Brudzinski's sign can be nonpathological as well in infants. There-

TABLE 5.—*Day of Illness on Which Paralysis Was Observed in a Group of 473 Paralytic Cases of Poliomyelitis Younger than One Year of Age*

Clinical Type of Poliomyelitis	Day When Paralysis Was First Observed												
	1	2	3	4	5	6	7	8	9	10	+10	Uncertain	Total
Spinal	36	44	75	69	42	17	21	7	—	4	8	27	350
Bulbar	1	2	4	—	1	—	—	1	—	—	—	3	11
Encephalitic	—	—	—	—	—	—	1	—	—	—	—	1	2
Spinal-bulbar	8	15	10	9	4	3	3	—	—	—	1	4	57
Spinal-encephalitic	—	1	—	—	—	—	3	1	—	—	—	—	5
Spinal-facial	4	2	4	3	1	3	2	1	—	1	1	1	22
Facial	2	4	4	1	2	—	1	—	—	—	—	1	15
Spinal-bulbar-encephalitic	3	2	2	—	—	—	—	—	—	—	—	—	7
Spinal-facial-encephalitic	1	—	1	—	—	—	1	—	—	1	—	—	4
Total	55	70	100	82	50	23	32	10	—	6	10	36	473

TABLE 6.—*Signs of Meningeal Irritation in Different Types of Poliomyelitis in 529 Cases of Poliomyelitis Younger than One Year of Age*

Clinical Type of Poliomyelitis	Signs of Meningeal Irritation			
	Present	Absent	Doubtful	Total
Nonparalytic	40	14	2	56
Spinal	138	207	15	350
Bulbar	3	6	2	11
Encephalitic	—	2	—	2
Spinal-bulbar	16	33	8	57
Spinal-encephalitic	2	2	1	5
Bulbar-encephalitic	—	—	—	—
Spinal-facial	10	12	—	22
Facial	6	8	1	15
Spinal-bulbar-encephalitic	—	3	4	7
Spinal-facial-encephalitic	1	3	—	4
Total	216	280	33	529

fore, when only the Brudzinski's sign was present, the patient was included in a group entitled "signs of meningeal irritation doubtful."

As seen in Table 6, in 53% of all the cases no signs of meningeal irritation were observed; in 6% there were doubtful signs, and in 41% definite signs were elicited.

The frequency of meningeal signs in the different clinical type groups was similar to the frequency of the whole group, with the exception of the nonparalytic group; 71% of the 56 cases in this group showed definite signs of meningeal irritation; 3.5% showed doubtful signs, and 25% showed no signs at all.

Laboratory Findings

The distribution of cases according to the number of white blood cells per cubic millimeter of cerebrospinal fluid at time of admission is presented in Table 7. About one-fifth of the cases had normal, slightly elevated, moderately elevated, markedly elevated, or very markedly elevated number. A similar pattern of distribution was observed among the spinal type and spinal-facial type patients. Fewer cases with a markedly elevated number of white blood cells were seen among the bulbar cases. More cases with markedly elevated number were observed among the spinal-encephalitic, spinal-bulbar, spinal-bulbar-encephalitic, and spinal-facial-encephalitic groups, and the nonparalytic group. In the last group 32% of the 53 examinations showed fewer than 70 white blood cells per cubic millimeter of cerebrospinal fluid; among those with more than 70 cells, 38% had more than 150 white blood cells per cubic millimeter. In the spinal-bulbar type group 46% of the patients had more than 150 white blood cells per cubic millimeter, and 26% had a markedly elevated number.

The distribution of cases according to the protein content of cerebrospinal fluid at

TABLE 7.—*Distribution of Cases of Poliomyelitis Under One Year of Age According to Number of White Blood Cells per Cubic Millimeter of Cerebrospinal Fluid*

Clinical Type of Poliomyelitis	Number of White Blood Cells per Cu. Mm. of CSF					
	Normal, 0-10	Slightly Elevated, 11-30	Moderately Elevated, 31-70	Markedly Elevated, 71-150	Very Markedly Elevated, >150	Totals
Nonparalytic	—	4	13	16	20	53
Spinal	65	65	60	66	56	312
Bulbar	—	2	2	1	1	6
Encephalitic	1	—	—	—	—	1
Spinal-bulbar	4	2	4	10	18	38
Spinal-encephalitic	1	—	—	—	2	3
Spinal-facial	5	4	3	3	5	20
Facial	4	3	3	1	3	14
Spinal-bulbar-encephalitic	—	—	1	1	2	4
Spinal-facial-encephalitic	—	—	—	3	1	4
Totals	80	80	86	101	108	455

TABLE 8.—*Distribution of Cases of Poliomyelitis Under One Year of Age According to Protein Content of Cerebrospinal Fluid on Admission to Hospital*

Clinical Type of Poliomyelitis	Protein Content in Mg. per 100 Ml. of CSF					
	Normal, <30 Mg.	Slightly Elevated, 31-40 Mg.	Moderately Elevated, 41-60 Mg.	Markedly Elevated, 61-80 Mg.	Very Markedly Elevated, >80 Mg.	Totals
Nonparalytic	26	13	10	1	—	50
Spinal	128	81	86	17	1	313
Bulbar	2	—	3	—	—	5
Encephalitic	1	—	—	—	—	1
Spinal-bulbar	16	10	9	1	—	36
Spinal-encephalitic	1	2	1	—	—	4
Spinal-facial	7	8	4	—	—	19
Facial	8	5	1	—	—	14
Spinal-bulbar-encephalitic	1	1	2	—	—	4
Spinal-facial-encephalitic	2	1	—	—	1	4
Totals	192	121	116	19	2	450

the time of admission to the hospital ward is presented in Table 8. In 192 patients the protein content was normal (42%); 121 patients had a slightly elevated protein content (27%); 116 had moderately elevated values (26%); 19 had a markedly elevated value, and 2 (0.5%) had a very markedly elevated content.

The spinal and spinal-bulbar type cases had a similar frequency distribution. Of the facial type cases, 58% had normal protein content and 35% had a slightly elevated content. No cases in this group had more than 60 mg. per 100 ml. of cerebrospinal fluid. Of the spinal-facial group of patients 63% had a higher than normal value. Among the nonparalytic cases 52% had normal values and 12% had higher than 40 mg. protein content per 100 ml. of cerebrospinal fluid.

TABLE 9.—*Correlation of Number of White Blood Cells and Quantity of Protein in Cerebrospinal Fluid Examined on Admission*

Clinical Type of Poliomyelitis	White Blood Cells per Cubic Millimeter of CSF	Proteins in Mg. per 100 Ml., of CSF						
		Normal, <30	Slightly Elevated 31-40	Moderately Elevated, 41-60	Markedly Elevated, 61-80	Very Markedly Elevated, >80	Not Done	Totals
Nonparalytic	Normal, <10	—	—	—	—	—	—	—
	Slightly elevated, 11-30	3	1	—	—	—	—	4
	Moderately elevated, 31-70	9	1	2	1	—	—	13
	Markedly elevated, 71-150	7	5	3	—	—	1	16
	Very markedly elevated, >150	7	6	5	—	—	2	20
	Total	26	13	10	1	—	3	53
Spinal	Normal, <10	28	10	22	5	—	—	65
	Slightly elevated, 11-30	28	16	18	3	—	—	65
	Moderately elevated, 31-70	30	13	16	1	—	—	60
	Markedly elevated, 71-150	21	24	18	2	1	—	66
	Very markedly elevated, >150	20	17	12	5	—	2	56
	Total	127	80	86	16	1	2	312
Bulbar	Normal, <10	—	—	—	—	—	—	—
	Slightly elevated, 11-30	1	—	1	—	—	—	2
	Moderately elevated, 31-70	1	—	—	—	—	1	2
	Markedly elevated, 41-150	—	—	—	1	—	—	1
	Very markedly elevated, >150	—	—	1	—	—	—	1
	Total	2	—	2	1	—	1	6

TABLE 9.—*Correlation of Number of White Blood Cells and Quantity of Protein in Cerebrospinal Fluid Examined on Admission* (Continued)

Clinical Type of Poliomyelitis	White Blood Cells per Cubic Millimeter of CSF	Proteins in Mg. per 100 Ml., of CSF: Normal, <30	Slightly Elevated 31-40	Moderately Elevated, 41-60	Markedly Elevated, 61-80	Very Markedly Elevated, <80	Not Done	Totals
Encephalitic	Normal, <10	1	—	—	—	—	—	1
	Slightly elevated, 11-30	—	—	—	—	—	—	—
	Moderately elevated, 31-70	—	—	—	—	—	—	—
	Markedly elevated, 71-150	—	—	—	—	—	—	—
	Very markedly elevated, >150	—	—	—	—	—	—	—
	Total	1	—	—	—	—	—	1
Spinal-bulbar	Normal, <10	2	1	1	—	—	—	4
	Slightly elevated, 11-30	1	1	—	—	—	—	2
	Moderately elevated, 31-70	4	—	—	—	—	—	4
	Markedly elevated, 71-150	5	3	1	1	—	—	10
	Very markedly elevated, >150	4	5	7	—	—	2	18
	Total	16	10	9	1	—	2	38
Spinal-encephalitic	Normal, <10	1	—	—	—	—	—	1
	Slightly elevated, 11-30	—	—	—	—	—	—	—
	Moderately elevated, 31-70	—	—	—	—	—	—	—
	Markedly elevated, 71-150	—	—	—	—	—	—	—
	Very markedly elevated, >150	—	1	1	—	—	—	2
	Total	1	1	1	—	—	—	3
Spinal-facial	Normal, <10	3	1	—	—	—	1	5
	Slightly elevated, 11-30	2	2	—	—	—	—	4
	Moderately elevated, 31-70	1	2	—	—	—	—	3
	Markedly elevated, 71-150	—	2	1	—	—	—	3
	Very markedly elevated, >150	1	1	3	—	—	—	5
	Total	7	8	4	—	—	1	20
Facial	Normal, <10	1	2	1	—	—	—	4
	Slightly elevated, 11-30	3	—	—	—	—	—	3
	Moderately elevated, 31-70	3	—	—	—	—	—	3
	Markedly elevated, 71-150	—	1	—	—	—	—	1
	Very markedly elevated, >150	1	2	—	—	—	—	3
	Total	8	5	1	—	—	—	14
Spinal-bulbar-encephalitic	Normal, <10	—	—	—	—	—	—	—
	Slightly elevated, 11-30	—	—	—	—	—	—	—
	Moderately elevated, 31-70	1	—	—	—	—	—	1
	Markedly elevated, 71-150	—	1	—	—	—	—	1
	Very markedly elevated, >150	—	—	2	—	—	—	2
	Total	1	1	2	—	—	—	4
Spinal-facial-encephalitic	Normal, <10	—	—	—	—	—	—	—
	Slightly elevated, 11-30	—	—	—	—	—	—	—
	Moderately elevated, 31-70	—	—	—	—	—	—	—
	Markedly elevated, 71-150	2	1	—	—	—	—	3
	Very markedly elevated, >150	—	—	—	—	—	1	1
	Total	2	1	—	—	—	1	4
All patients	Normal, <10	36	14	24	5	—	1	80
	Slightly elevated, 11-30	38	20	19	3	—	—	80
	Moderately elevated, 31-70	49	16	18	2	—	1	86
	Markedly elevated, 71-150	35	37	23	4	1	1	101
	Very markedly elevated, >150	33	32	31	5	—	7	108
	Total	191	119	115	19	1	10	455

TABLE 10.—*Distribution of Cases of Poliomyelitis Under One Year of Age According to Number of White Blood Cells per Cubic Millimeter of Cerebrospinal Fluid After Fall of Temperature to Normal*

	Number of White Blood Cells per Cu. Mm. of CSF					
Clinical Type of Poliomyelitis	Normal, 0-10	Slightly Elevated, 11-30	Moderately Elevated, 31-70	Markedly Elevated, 71-150	Very Markedly Elevated, >150	Totals
Nonparalytic	39	1	4	—	—	44
Spinal	200	22	5	2	—	229
Bulbar	—	—	—	—	—	—
Encephalitic	—	—	—	—	—	—
Spinal-bulbar	8	—	—	—	—	8
Spinal-encephalitic	2	—	1	—	—	3
Spinal-facial	15	1	—	—	—	16
Facial	6	2	—	1	—	9
Spinal-bulbar-encephalitic	—	—	1	—	—	1
Spinal-facial-encephalitic	2	—	—	—	—	2
Totals	272	26	11	3	—	312

In 445 patients both the number of white blood cells and the protein content of the sample of cerebrospinal fluid withdrawn at time of admission to the hospital were examined. Half the number of patients with normal number of white blood cells had normal protein content as well. The higher the number of cells, the lower was the number of cases with normal protein content, reaching 33% of those with very markedly elevated number of cells (Table 9).

The number of white blood cells in the cerebrospinal fluid after the fall of temperature to normal was normal in 272 of the 312 cases (87%), slightly elevated in 26 (8%), moderately elevated in 11 (4%), and markedly elevated in 3 (1%). There were no patients with a very markedly elevated number of cells (Table 10).

The protein content of the cerebrospinal fluid after the fall of temperature to normal was normal in 134 patients (43%), slightly elevated in 93 (30%), moderately elevated in 69 (22%), markedly elevated in 13 cases (4%), and very markedly elevated in 3 (1%) (Table 11).

The protein content of the cerebrospinal fluid after the fall of temperature to normal declined to normal in about a fourth of the patients with a slightly elevated level at the time of the first examination, as well as in more than a fourth of those with moderately

TABLE 11.—*Distribution of Cases of Poliomyelitis Under One Year of Age According to Protein Content of Cerebrospinal Fluid After Fall of Temperature to Normal*

	Protein Content in Mg. per 100 Ml. of CSF					
Clinical Type of Poliomyelitis	Normal, <30 Mg.	Slightly Elevated, 31-40 Mg.	Moderately Elevated, 41-60 Mg.	Markedly Elevated, 61-80 Mg.	Very Markedly Elevated, >80 Mg.	Totals
Nonparalytic	34	5	3	—	1	43
Spinal	79	81	59	10	2	231
Bulbar	—	—	—	—	—	—
Encephalitic	—	—	—	—	—	—
Spinal-bulbar	5	—	2	1	—	8
Spinal-encephalitic	—	2	1	—	—	3
Spinal-facial	8	3	4	1	—	16
Facial	7	2	—	—	—	9
Spinal-bulbar-encephalitic	—	—	—	1	—	1
Spinal-facial-encephalitic	1	—	—	—	—	1
Totals	134	93	69	13	3	312

TABLE 12.—*Correlation of Presence of Meningeal Irritation Signs with Changes of Cerebrospinal Fluid Protein Content and Number of White Blood Cells*

A. White Blood Cells

No. of WBC per Cu. Mm.	Signs of Meningeal Irritation, No. of Cases			
	Present	Absent	Doubtful	Totals
<10	25	52	3	80
11-30	32	48	—	80
31-70	37	43	6	86
71-150	48	48	5	101
>150	55	48	5	108
Totals	197	239	19	455

B. Protein Content

Protein Content of CSF, Mg. per 100 Ml.	Signs of Meningeal Irritation, No. of Cases			
	Present	Absent	Doubtful	Totals
<30	90	99	3	192
31-40	46	69	6	121
41-60	50	57	9	116
61-80	9	8	2	19
>80	1	1	—	2
Totals	196	234	20	450

elevated level. An increase of the protein content occurred in about a third of the patients with a normal protein level at the time of admission and in a few cases with an elevated level.

Correlation of Signs of Meningeal Irritation with Cerebrospinal Fluid Laboratory Findings

The correlation between the presence or absence of signs of meningeal irritation and the presence and degree of pathological findings in the cerebrospinal fluid is presented in Table 12. It is evident that no correlation could be established between these clinical findings and laboratory results. Almost half the cases of each group, from those with normal to those with very markedly elevated white blood cells or protein content presented signs of meningeal irritation, and the other half presented no signs.

Mortality

Seventy-seven patients died. Eleven had spinal type cases. In seven of these death was caused by lung infection, complicating widespread intercostal muscle and diaphragm paralyses. One patient died in acute asphyxia shortly after the admittance to the ward. The postmortem examination revealed poliomyelitic changes of the whole length of the spinal cord, but no changes were observed in the medulla. In three cases the course of poliomyelitis was complicated by severe gastrointestinal disturbance and electrolyte imbalance, which probably contributed to the fatal outcome (Table 13).

Summary and Conclusions

During the first seven years of a poliomyelitis epidemic in Israel (1950-1956), 529 infants with poliomyelitis younger than one year of age were treated at Pediatric Department B of Rambam Government

TABLE 13.—*Mortality Among Cases of Poliomyelitis Under the Age of One Year*

Age Group, Mo.	Spinal	Encephalitic	Bulbar	Spinal-Encephalitic	Spinal-Bulbar	Spinal-Bulbar Encephalitic
1	—	—	—	—	—	—
2	1	—	1	—	1	—
3	1	—	1	—	1	1
4	1	—	—	—	3	—
5	—	2	1	—	2	—
6	—	—	2	—	6	1
7	1	—	1	—	10	1
8	—	—	—	—	5	—
9	—	—	2	1	3	2
10	2	—	—	—	4	—
11	—	—	1	—	6	1
12	5	—	1	—	7	—
Totals	11	2	10	1	47	6

Hospital in Haifa. The clinical and laboratory findings in this group of patients are described.

No correlation could be established between the severity of the disease and the changes in the cerebrospinal fluid components. No constant pattern was observed in the different clinical type groups. The laboratory examination of the cerebrospinal fluid did not follow the established pattern of "pleocytosis with normal protein content" at the beginning of the disease and "normal white blood cell count with an elevated protein content" later in the disease. The significance of this observation can be evaluated when further reports dealing with poliomyelitis in infants confirm it. The dynamics of the cerebrospinal fluid changes during the acute illness could not be predicted in this group of patients.

No correlation could be established between the presence of signs of meningeal irritation and the presence and degree of pathological changes of the cerebrospinal fluid.

1135 Adams St. (6).

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Case Reports

Hypoplasia of the Left Heart Complex

Report of Two Cases Showing Premature Obliteration of the Foramen Ovale and Differential Cyanosis

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The object of this paper is to report two infants with hypoplasia of the left side of the heart and ascending aorta, premature obliteration of the foramen ovale, and a differential cyanosis of a very unusual distribution. The cyanosis involved the skin of the entire body with the exception of the right upper quadrant.

Report of Cases

CASE 1.—A white boy was admitted to the hospital at the age of one day because of cyanosis and rapid respirations. At birth, the infant did not breathe for five minutes and was cyanotic. Once respiration became established, it remained rapid; his color improved, but cyanosis was noted several times during the first day.

His weight was 8 lb. 4 oz. The temperature was 100 F. The pulse rate was 160, and the respirations were 36 per minute. No blood pressure could be obtained in the arms or legs. No cardiac murmur was heard, and the lungs were clear. The skin of the entire body was cyanotic except for the right upper quadrant of the trunk, the right side of the head and neck, and the right arm, which were of normal pink color (Fig. 1). Anteriorly, the line of demarcation between the cyanotic and the normally colored skin ran along the midline of the face, neck, chest, and upper abdomen; it then ran across the right upper abdomen, just above the level of the umbilicus; posteriorly, it followed the median line of the head and neck and the vertebral margin of the right scapula. The right side of the chest included between the anterior and posterior axillary lines showed some cyanosis. The line of demarcation was remarkably

Submitted for publication Oct. 20, 1958.

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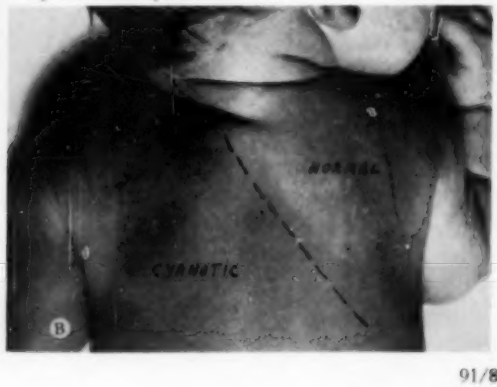


Fig. 1 (Case 1).—*A*, anterior view; *B*, posterior view. In both patients, the right side of the face, the right shoulder and arm, and the right upper quadrant of the trunk were of normal pink color, whereas the rest of the body was cyanotic. The line of demarcation between the normal and the cyanotic skin, not clearly reproduced in these photographs, is indicated by the interrupted line.

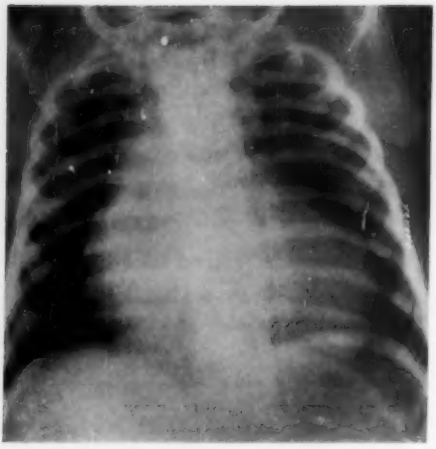


Fig. 2 (Case 1).—Posteroanterior roentgenogram of the chest taken at one day of age.

straight and sharp over the sternum and across the right side of the abdomen anteriorly but less sharply defined elsewhere (particularly in the axilla).

In the hospital the infant appeared sleepy, took his feedings poorly, and vomited small amounts frequently. The pulse rate ranged between 100 and 180 per minute. The respirations were shallow and became progressively more rapid. The cyanosis also increased progressively in intensity, especially when out of oxygen, but its distribution remained the same as on admission. The infant developed puffiness of the face and then generalized edema, without appreciable enlargement of the liver or distention of the neck veins. On the third hospital day, at 4 days of age, he suddenly died apparently after aspirating his formula.

The laboratory findings included a hemoglobin of 25.6 gm. % and a red cell count of 6,500,000. The chest roentgenograms, taken on admission (Fig. 2), showed considerable enlargement of the heart; the cardiac apex was rounded and elevated; the lungs were clear, and the intrapulmonary vasculature was thought to be reduced in caliber. The electrocardiogram revealed left ventricular hypertrophy (Fig. 3). The therapy consisted of oxygen, digitalis, mercurial diuretics, and antibiotics.

At autopsy, the lungs contained multiple scattered areas of collapse, and fat debris was present in the bronchi, bronchioles, and alveoli. The heart weighed 40 gm. The right atrium and right ventricle were large, but their walls were of of average thickness. The foramen ovale was completely obliterated. The tricuspid and pulmonary valves were normal. The pulmonary artery was relatively large. The ductus arteriosus was widely patent. The left atrium had a small lumen and thick walls; its endocardium was thick and white. The mitral valves were thick, but the

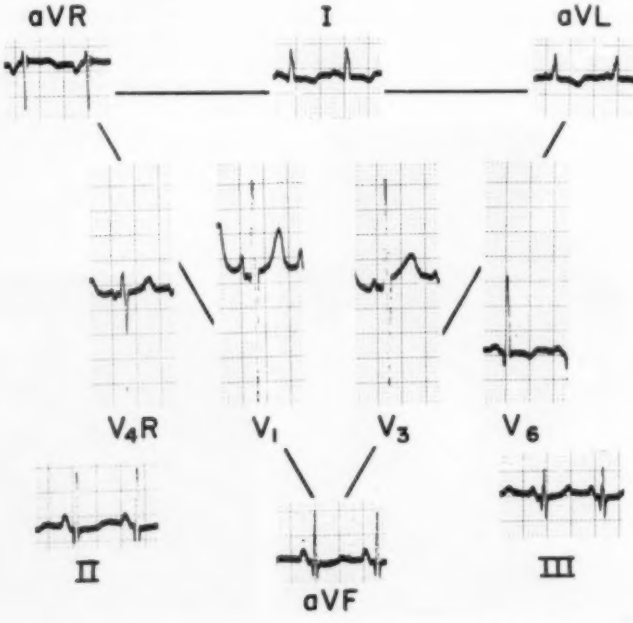


Fig. 3 (Case 1).—Electrocardiogram taken at 2 days of age, showing evidence of left ventricular hypertrophy.

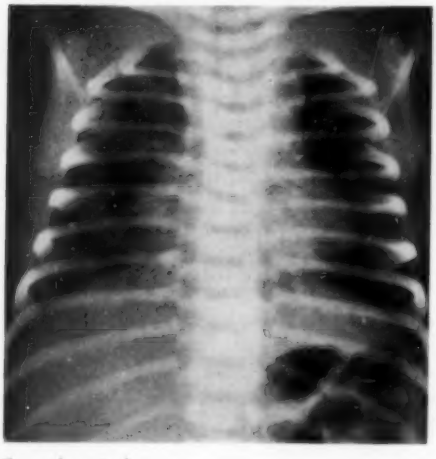
mitral orifice was not unusual in size. The left ventricular cavity was relatively small as compared with the thickness of its walls (1 cm.); its endocardial lining was thick, dense, and whitish. The aortic orifice was greatly reduced in size, measuring 1 mm. in diameter; its valve leaflets were fused. The aorta, from its origin to the junction with the ductus arteriosus, was abnormally small but gave off the normal branches. Beyond the ductus arteriosus, the aorta had a normal caliber.

CASE 2.—A white girl was referred to the hospital at the age of one day because of cyanosis and slight periorbital edema, which became apparent immediately after birth.

Her weight was 6 lb. 13 oz. The pulse rate ranged between 180 and 200 per minute. The respiratory rate was 60 per minute, and the respirations were deep and gasping. The femoral pulses were palpable. There was mild periorbital edema. The skin was cyanotic throughout, excepting the right upper quadrant of the body, which was of normal pink color. The distribution of the cyanosis was the same as described in Case 1. The lungs were clear. A Grade 2 systolic murmur was heard in the second to third interspace, to the left of the midline. The second heart sound in the pulmonic area was loud. The liver edge was felt 3 fingerbreadths below the costal margin.

In the hospital, the respirations became increasingly more labored and the tachycardia increased. The cyanosis increased gradually in intensity both in and out of oxygen, but it maintained the same distribution as on admission. During the second hospital day, the infant's respirations dropped suddenly to 2-6 per minute, and after a short period of time she died, at the age of 3 days.

Fig. 4 (Case 2).—Posteroanterior roentgenogram of the chest taken at 2 days of age.



The laboratory findings included a hemoglobin of 15.1 gm. % and a red cell count of 3,770,000. The chest roentgenograms taken on the second hospital day showed a cardiovascular silhouette of normal size and shape (Fig. 4). The vascular markings in the lungs were slightly prominent, and there was some infiltration in the right middle lobe. The electrocardiogram revealed marked right ventricular hypertrophy. The therapy included oxygen, digitalis, mercurial diuretics, and morphine.

At autopsy, the lungs showed diffuse edema and multiple scattered areas of collapse with focal emphysema and hemorrhages. There was considerable hepatomegaly. The heart was moderately enlarged. The right atrium and right ventricle were large, but their walls were of normal thickness. The foramen ovale was completely obliterated. On the right surface of the interatrial septum, at the site of the foramen ovale, there was a sac-like projection which ran forward and ended blindly. The tricuspid and pulmonary valves were normal. The pulmonary artery was enlarged. The ductus arteriosus was patent and opened widely into the descending aorta. The left atrium had a small lumen and thick walls, but its endocardial surface had a normal appearance. The mitral orifice was extremely small, and its valve leaflets were sclerotic. The cavity of the left ventricle was likewise very small, and its lining was thick, dense, and whitish. The aortic orifice was greatly reduced in size, and its valves were sclerotic. The aorta, from its origin to the insertion of the ductus arteriosus, was abnormally small; however, it gave off the normal branches. A further narrowing of the aorta was present immediately proximal to the ductus arteriosus. Distal to the ductus arteriosus, the aorta was normal in caliber.

Comment

These two patients are of interest in that they showed a combination of three unusual findings, namely, hypoplasia of the left side of the heart and ascending aorta, premature obliteration of the foramen ovale, and a cyanosis which involved only three-fourths of the body surface. These three features will be discussed briefly.

Hypoplastic Left Heart Complex.[1-6]—This is a rather infrequent combination of congenital anomalies of the cardiovascular system characterized mainly by an often extreme underdevelopment of the left cardiac chambers—particularly the ventricle—and an atresia or stenosis of the aortic and/or mitral valves. In the majority of instances, either both these valves are in-

volved or the involvement is severe in the aortic valve but mild or even absent in the mitral orifice. The combination of severe mitral involvement and a relatively normal aortic valve is rare. The ascending aorta and aortic arch are almost always hypoplastic; in cases of isolated mitral atresia or severe stenosis, the ascending aorta tends to be more normal in size. Endocardial fibroelastosis of the left ventricle, and often also of the left atrium, is a frequent finding. The foramen ovale and the ductus arteriosus are usually patent, and not uncommonly there is also a ventricular or an atrial septal defect. A ventricular septal defect is particularly frequent when there is a mitral atresia or severe stenosis without any gross deformity of the aortic valve. The left auricular appendage is often large. The right cardiac chambers and the pulmonary artery tend to be enlarged and hypertrophied. In most cases, the coronary arteries have a normal origin and distribution.

Patients with this condition usually die during the first week of life; they seldom survive the first month. The survival seems to be slightly longer when the aortic valves are not severely affected. Once symptoms become apparent, the general condition of the patient deteriorates rapidly. The main symptoms and findings are dyspnea, tachycardia, cyanosis, and right-sided congestive failure, which is refactory to the usual forms of therapy. At first, the cyanosis may be absent or minimal, but as time goes on it tends to become severe. A precordial systolic murmur is present in many instances. The electrocardiogram usually shows an abnormal degree of right ventricular hypertrophy. Electrocardiographic evidence of left ventricular hypertrophy, such as noted in Case 1 of this report, is rare and difficult to explain. Roentgenographically, the cardiac shadow may be normal in size or variously enlarged; terminally it tends to be grossly enlarged. The intrapulmonary vasculature also varies from slightly increased, especially at the hila, to normal.

Premature Obliteration of the Foramen Ovale.[7,8]—According to Patten,[9] the foramen ovale does not close normally before the last third of the first year of life. Complete obliteration of the foramen before the third month of postnatal life is an exceedingly rare anomaly. Fewer than 20 such cases (including the 2 here reported) have been observed so far. The majority of these patients died a few hours or days after birth; some were stillborn. The longest survival was five weeks. The major clinical symptoms and findings were dyspnea, cyanosis, and occasionally edema. At autopsy, this premature obliteration of the foramen ovale was accompanied by essentially the same cardiovascular malformations described in "hypoplasia of the left heart complex." The left cardiac chambers were underdeveloped, and the ascending aorta and aortic arch tended to be hypoplastic. Left-side endocardial fibroelastosis and patency of the ductus arteriosus were practically always present. Not uncommonly, the mitral and/or aortic valves were atretic, stenotic, or defectively developed. A ventricular septal defect was present in some instances. The right cardiac chambers tended to be enlarged and hypertrophied. Occasionally, similar changes have been observed also in association with a probe-patent but functionally closed foramen ovale.

It has been suggested[8] that "premature closure of the foramen ovale" is a separate pathological and clinical entity and that the deranged intracardiac blood flow during fetal life, resulting from the obliteration of this foramen, is responsible for all the other associated cardiovascular malformations. However, in view of the close similarity between this series of malformations and those of "hypoplasia of the left heart complex," the possibility still remains that a prematurely obliterated foramen ovale is not the primary lesion but only an anomaly uncommonly associated with the syndrome of the hypoplastic left heart. Whether premature closure of the foramen ovale can occur also as an isolated lesion and in entirely asymptomatic persons is unknown.

Differential Cyanosis.—Since the noncyanotic quadrant of the skin in these patients corresponded exactly to the cutaneous distribution of the arteries originating from the innominate,[10] it is very likely that this type of differential cyanosis was due to the fact that well-oxygenated blood from the left ventricle and ascending aorta reached the innominate artery and all its branches, whereas the skin of the rest of the body received most of its blood supply from the right ventricle through the widely patent ductus arteriosus. A diagram of this type of circulation is outlined in Figure 5. The straight and well-defined line of demarcation over the sternum and right upper abdomen, anteriorly, and the poor definition of this line in other areas, was presumably the result of the different degree of overlap of the cutaneous arterial vessels, which is normal for these regions.

Theoretically, cyanosis of an identical distribution is expected to occur in patients affected by patency of the ductus arteriosus in association with an interruption of the aortic arch between the innominate artery and the left carotid artery. However, this was not present in the only two[11,12] instances of such malformations which could be found in the available literature. In Dorney's case[11]—a Negro boy aged 5 years—there was cyanosis and clubbing, but these were limited to the left hand and both feet. In Weisman's case[12]—a newborn infant—the cyanosis was generalized, but there was also a ventricular and an auricular septal defect which presumably accounted for it. As is known, a differential cyanosis in which the upper half of the body, especially the right hand, is pink, whereas the lower extremities are blue, is seen occasionally in patients affected by coarctation of the aorta associated with patent ductus arteriosus below the coarctation,[13] and in an occasional patient with patency of the ductus arteriosus complicated by peripheral pulmonary artery disease and reversal of the shunt.[14,15] A search of the literature on this subject, however, has failed to reveal any such case in which there was a cyanosis identical in distribution to that present in our two patients.

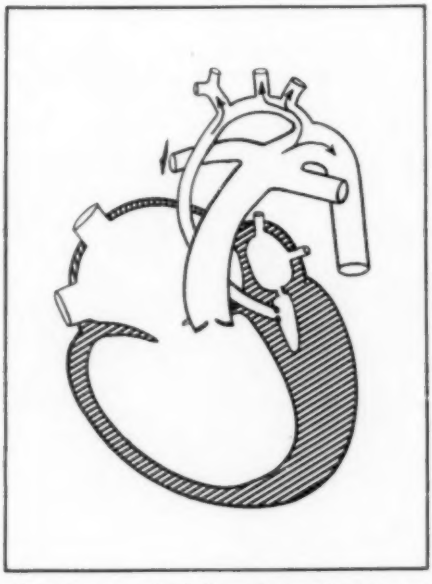


Fig. 5.—The circulation of the blood in the great vessels (arrows), which is postulated as an explanation of the unusual type of differential cyanosis presented by the two patients reported in this paper.

Summary

Two instances of hypoplasia of the left side of the heart and evidence of premature obliteration of the foramen ovale are reported. In both patients, the skin of the right upper quadrant of the body was of normal pink color, whereas the rest of the body was cyanotic. The underlying cardiovascular malformations and this type of differential diagnosis are discussed briefly.

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Addendum

Since this report was submitted for publication, the following paper has appeared: Noonan, J. A. and Nadas, A. S.: The Hypoplastic Left Heart Syndrome: An Analysis of 101 Cases. Pediat. Clin. North America pp. 1029-1056, November, 1958.

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Sarcoma Botryoides (Embryonal Rhabdomyosarcoma) of the Anus

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Sarcoma botryoides is a tumor that occurs predominantly in the urogenital region, chiefly of infants and children. Although it is considered by many to be a form of rhabdomyosarcoma, there has been no dearth of names used in classifying and describing it, as shown by MacFarland,[1] who in 1935 collected 119 synonyms.

Sarcoma botryoides is a rare tumor and in an extraurogenital location is even rarer. This is emphasized by the excellent reviews of extraurogenital tumors of this type made by Horn et al.[2] and Farinacci et al.[3] Neither of these groups refer to a reported case of sarcoma botryoides arising from the anus, and in a further search of the literature and personal communication with pathologists we have not been able to learn of any other instance of sarcoma botryoides in this location.

Submitted for publication Oct. 16, 1958.
Armed Forces Institute of Pathology.

Report of Case

A Negro male infant, 2 months of age, was first seen in December, 1948, because of a small "growth" in the anus. The mother had first noticed it three weeks previously, but could not state with certainty whether the mass had been present at birth. The infant appeared to be healthy and the only abnormality was what was described as a pedunculated "papilloma" of the anus. A cautery excision of the "papilloma" was performed under local anesthesia. Hemorrhage was controlled by electrocoagulation. The postoperative course was uneventful, and the patient was discharged 48 hours after operation.

The specimen submitted to the laboratory consisted of a formalin-fixed ovoid mass, 2.5×1.5×1.5 cm. It had a polypoid configuration, and one surface was covered by smooth glistening membrane.

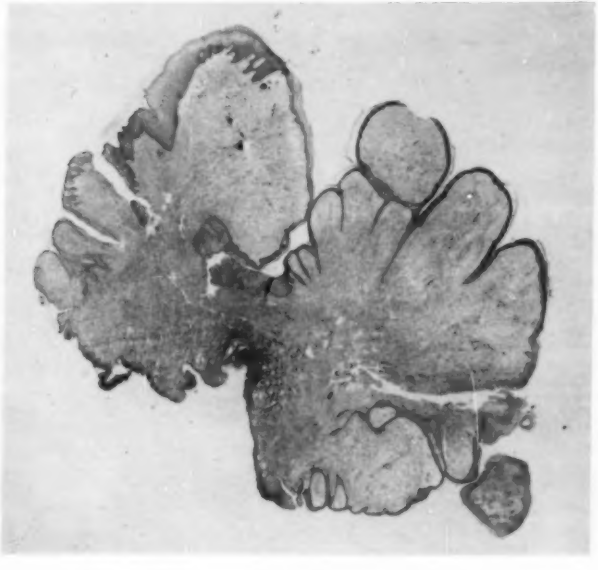

Fig. 1.—Cross section of tumor. The polypoid configuration is readily apparent. Hematoxylin and eosin; ×6. (AFIP Acc. 236361)

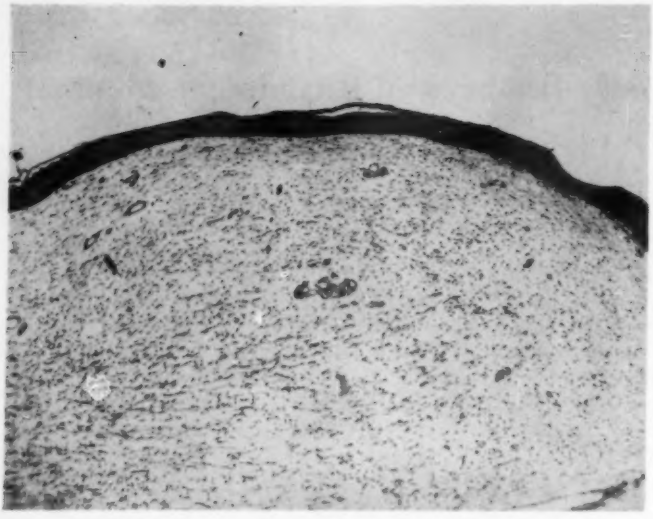

Fig. 2.—Stratified squamous epithelium covers a loosely knit edematous stroma. Hematoxylin and eosin; reduced about 8% from mag. × 50. (AFIP Acc. 236361)

On cut surface the fibrous stroma was edematous.

Microscopic examination revealed papillary and polypoid projections covered by stratified squamous epithelium. In several places the epithelium was ulcerated and the base infiltrated with polymorphonuclear leukocytes. The core of the polypoid projections was composed of spindle-shaped, stellate "strap," and undifferentiated cells, associated with edema and scattered lymphocytes. Blood vessels were numerous and their walls often thickened by hyperplastic appearing cells. The initial diagnosis was granuloma pyogenicum, but when the slides were reviewed examination revealed rhabdomyoblasts with cross striations, and the interpretation was changed to sarcoma botryoides.

The child was not seen again until May, 1949, when he was admitted to another hospital with the clinical diagnosis of hemangioma of the buttocks. A biopsy was reported as "capillary hemangioma," and local excision was performed. In April, 1952, the child was returned to the hospital, and at this time a diagnosis of "angiosarcoma" of the buttocks with metastasis was made. In September he was again admitted because of retention of urine caused by involvement of

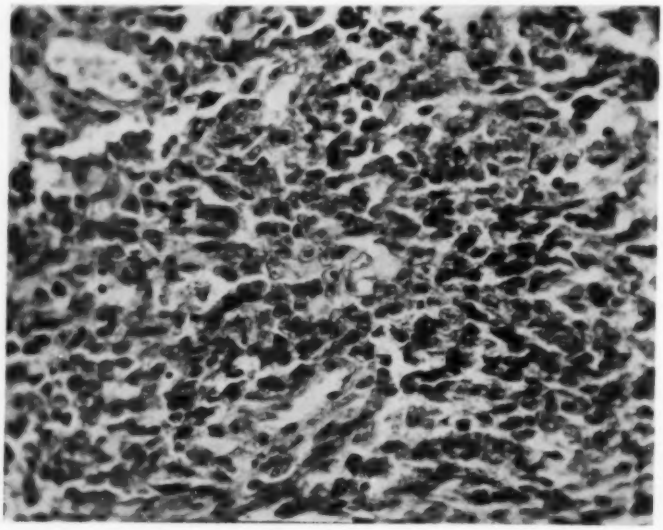

Fig. 3. — Densely packed, pleomorphic cells in a subepithelial area (cambium layer). Hematoxylin and eosin; reduced about 8% from mag. × 305. (AFIP Acc. 236361)

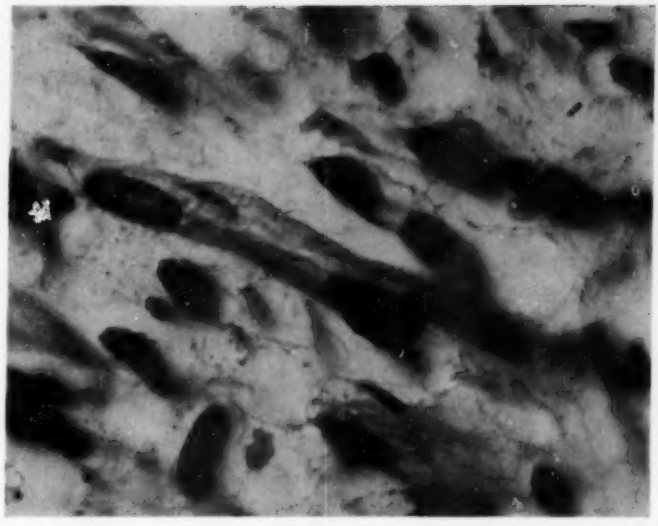

Fig. 4.—Rhabdomyoblasts showing horizontal and vertical striations. Hematoxylin and eosin; reduced about 8% from mag. ×1,000. (AFIP Acc. 236361)

the urethra by sarcoma metastatic from the buttocks. A suprapubic cystotomy was performed. A month later he was admitted for the last time because of acute intestinal obstruction caused by direct extension of sarcoma from the buttocks. A transverse colostomy was performed, and the patient was discharged three weeks later. He died in December, 1952. Permission for an autopsy was not obtained.

Comment

This neoplasm revealed the classical diagnostic criteria of sarcoma botryoides. It had an edematous polypoid (grape-like) configuration. Microscopically, cross striations were seen in the cells of a polymorphous edematous and myxoid stroma. In a few areas there was a densely cellular subepithelial zone (cambium layer). In addition scattered foci of inflammatory cells and macrophages were present. Cross striations may not be a feature and are not a prerequisite for diagnosis, but when present, they enable a clear-cut decision to be made. Several of the published reports of lesions similar to ours disclose that these also were initially misdiagnosed as a papilloma or an inflammatory polyp. Farinacci et al. aptly stated that the innocent microscopic appearance is only superficial.

The earlier investigators emphasized the universal rule of local recurrence of sarcoma botryoides but did not record a large percentage of distant metastases. In fact, Ulfelder and Quan [4] in 1947 stated that metastases were rare. The recent reports of extraurogenital lesions have noted distant metastasis to be fairly common. In our patient there was widespread local infiltration and probably local metastasis. Since no autopsy was done, no statement can be made regarding distant metastases.

Ober and Edgcomb [6] referred to a female patient with a lesion of the urogenital tract, who had survived for five years, and Horn's group reported a seven-year survival in a patient with an extraurogenital lesion. Our patient survived four years after the initial local excision. Mostofi and Morse[8] noted that patients with sarcoma botryoides of the bladder usually died within 24 months. When feasible, perhaps prompt wide excision would give better results.

The histogenesis of this neoplasm has received a great deal of attention. The concensus today is that sarcoma botryoides is congenital and that postnatal influences are nil. Rakov,[5] in 1937, expressed a distaste for the term rhabdomyosarcoma, because to him it implied that the origin was from mature striated muscle cells. Ober and Edgcomb [6] defined it as derived from mesen-

chyme. Willis[7] considered its origin to be from young tissue that has never differentiated. Mostofi and Morse,[8] using similar terminology, defined the origin from multipotential embryonic tissue, and believed that rhabdomyoblasts with cross striations appeared only in the better-differentiated lesions. They also reiterated that the gross grape-like structures, per se, justified the term, sarcoma botryoides. In this respect, Horn et al. stressed a previously published opinion that this characteristic gross form is possible only when the site of origin is such that ample space for free expansion is available.

Stout preferred to place this tumor in a group designated malignant mesenchymomas.[9] He considered this particular lesion to be capable of presenting the following histological pictures: rhabdomyosarcoma, myxoma, and mixed mesodermal tumor.[10] In regard to the rhabdomyoblastic cell he recognized three different forms:[11] the rounded-cell type, the strap-shaped cell with two or more nuclei arranged in tandem, and the racquet-shaped cell with a single nucleus at one end. All of these forms have eosinophilic cytoplasm that is usually granular, and a few usually contain either cross striations or longitudinal myofibrils.

Summary and Conclusion

A child with sarcoma botryoides of the anus is reported. Following a simple surgical removal there was recurrence and death four years later. Early recognition and radical removal of the tumor is imperative if treatment is to be successful.

Walter Reed Army Medical Center (25) (Dr. Helwig).

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Acute Perforative Thromboendocarditis Complicating Staphylococcal Osteomyelitis

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In spite of the existence of a powerful armamentarium of antibiotics, acute osteomyelitis continues to present a challenge as regards both health and life. Since the initial claims of the modern antibiotic era, it is now generally agreed that acute osteomyelitis is principally a surgical problem. Basic principles of early diagnosis, early antibiotic therapy, and, when necessary, early surgical intervention, continue to be fundamental. These, if correctly applied, may help to avert the occasional death. The following is a case in which these principles were not adhered to, a case which ultimately proved fatal owing to septicemic sequelae.

Report of Case

The patient was a girl aged 10 who had been epileptic since infancy. After one of these epileptic attacks, she began to complain of pain in the left leg just below the knee. The pain soon disappeared, but three days later she again had an attack of severe pain in the same location, accompanied by a high temperature. The family physician was called in and started penicillin therapy; however, because of neglect by the family, this was discontinued after one day. Three days later the child was still febrile and began to complain of pain below the right knee as well. The physician was called again and once more prescribed penicillin. This too was not administered. On his third visit, nine days after the onset of the complaint, the physician found the child extremely ill and sent her to hospital.

On admission, the anterior aspect of the upper third of each leg was seen to be markedly swollen and red; fluctuation was present. The child's temperature was 39.7 C (100 F); respiration was rapid, and she breathed with the accessory muscles of respiration; scattered rhonchi and rales were heard at both lung bases. The pulse rate was 140 per minute, irregular, with extrasystoles. Examination of the heart revealed no abnormal findings. Blood pressure was 110/70. There was no abnormal tenderness in the abdomen; the liver and spleen were not found to be enlarged. Neurological examination was negative. Blood examination: leukocytes 15,000 per cubic millimeter; red blood cells 3,900,000 per cubic millimeter; hemoglobin 10.4 gm. %. X-ray examination of the chest and the legs showed no abnormality.

Further Course.—At operation, performed on the day of admission to hospital, large subperiosteal abscesses were found around both tibiae. The abscesses were incised, and wide openings were left for drainage. Culture of the pus revealed Staphylococcus aureus, insensitive to penicillin but sensitive to chloramphenicol (Chloromycetin), oxytetracycline (Terramycin), and chlortetracycline (Aureomycin). Antibiotic therapy and intravenous fluids, including whole blood, were instituted at the time of operation. However, the child remained febrile with a fluctuating temperature. On the fourth postoperative day she became cyanotic with marked respiratory distress. Physical examination revealed generalized cardiac enlargement, marked friction rub over the precordium and dullness at both lung bases. The liver was palpable 3 cm. below the right costal margin. X-ray examination confirmed the cardiac enlargement and revealed shadowing at both lung bases. ECG showed a low QRS complex with an elevated ST segment. In coordination with Prof. H. Milwidsky from the Department of Thoracic Surgery a diagnosis of acute pulmonary congestion and pericarditis with effusion was made. A pericardial tap produced 100 cc. of serous fluid, which was sterile on culture.

During the subsequent 24 hours, the child showed some improvement and then became cyanotic with respiratory distress. The pericardial sac was once more punctured, and 200 cc. of cloudy fluid was withdrawn. On culture, this fluid produced S. aureus of a strain similar to that isolated from the leg abscess and with the same resistance to antibiotics as mentioned above. The child's condition failed to improve; a pericardiostomy was, therefore, performed for purposes of drainage, but her condition continued to deteriorate, and she

Submitted for publication Oct. 10, 1958.

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died in cardiac failure, a fortnight after her admission to hospital.

Autopsy Findings

Heart.—The parietal serous pericardium was diffusely thickened by edema and fibropurulent exudate. It was adherent to the epicardial surface and caused obliteration of most of the lumen of the pericardial sac. The residual pericardial cavity contained about 10 cc. of sanguineous pus. The heart was moderately enlarged owing to hypertrophy, without dilatation of the left ventricle. A thrombotic vegetation was found attached by a stalk to the atrial aspect of the anterior mitral leaflet (Fig. 1.). The body of the vegetation measured 1.5 cm. in diameter, and dissection at the base of the stalk showed that it occluded a round perforation of the leaflet 5 mm. in diameter with irregular necrotic edges (Fig. 2.). The perforation

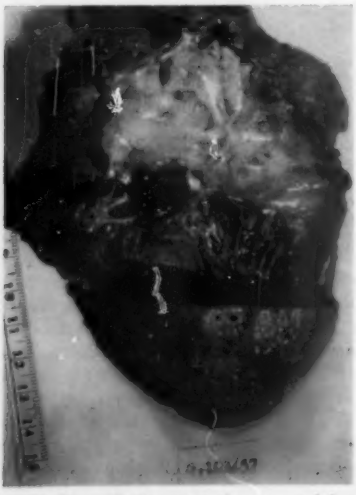


Fig. 1.—Thrombotic vegetation on atrial aspect of anterior mitral leaflet.

was found to have been the result of erosion of the leaflet by a myocardial abcess located within the uppermost part of the anterior wall of the left ventricle near the atrioventricular groove. This abscess measured 1.5 cm. in diameter; it had also eroded the overlying epicardium and had extended to the right of the interventricular septum into the subepicardial fatty tissue lying in front of the aortic and pulmonary valvular openings, without affecting the latter.

Lungs.—Moderate acute bilateral emphysema with confluent yellow foci of consolidation throughout both lungs.

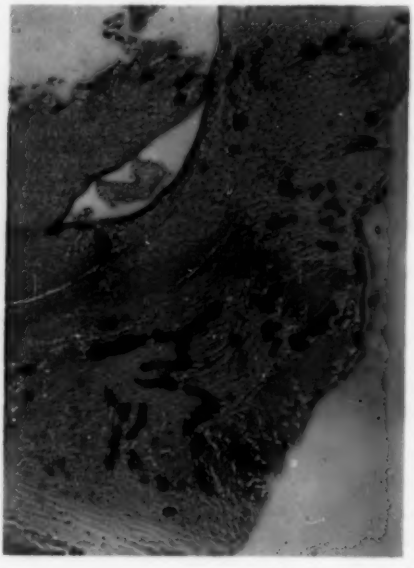
Spleen.—Enlarged, showing marked hyperplasia of the red pulp and two recent infarctions with yellow central softening.

Fig. 2.—Perforation of anterior mitral leaflet seen after removal of thrombotic vegetation shown in Figure 1.

Kidneys.—Several recent cortical infarctions were found in both kidneys; each infarction presented a central yellowish softening.

Other Organs.—Nothing abnormal was detected.

Fig. 3.—Histological section through anterior mitral leaflet. The darker bank across the picture shows the edges of the perforation covered by necrotic material and fibrin (lower half of picture). Hematoxylin and eosin; × 38.



Histological Findings

Tibiae.—Sections from both tibiae at the sites of the surgical incisions showed the typical picture of acute purulent osteomyelitis.

Anterior Mitral Leaflet.—The edges of the perforation consisted of young granulation tissue covered, near the eroded margin, by necrotic material and fibrin. Large accumulations of Gram-positive cocci were present.

Necrotic Area in Upper Part of Anterior Ventricular Wall (Fig. 3).—This presented the histological picture of a suppurative myocardial infarction infected by Gram-positive cocci. Sections from the pericardium revealed fibrinopurulent pericarditis, occasionally organized by granulation tissue.

The histological examination of the spleen and the kidneys confirmed the macroscopic diagnosis of infarctions. Many Gram-positive cocci were seen.

Comment

The anterior wall of the left cardiac ventricle, close to the atrioventricular groove, is a common location for pyemic myocardial abscesses.[1] According to Pirani,[2] the predilection is to be explained by the particular structure of the myocardial aortic junction and by the presence of abundant subepicardial fat, giving this region less resistance. From this area the septic process may easily extend to the myocardial tissue near the aortic ring and thence to the adjoining anterior mitral leaflet; or it may follow the loose fibrous tissue around the large branches of the left coronary artery and thus reach the nearby pericardium by contiguity, causing pericarditis.[3]

Summary

A case is presented of a child with neglected acute osteomyelitis of both tibiae. The early treatment was inadequate, and she was hospitalized only nine days after the onset of her illness. Treatment then consisted of operation and intensive antibiotic therapy. The girl died 14 days after admission with congestive heart failure and respiratory distress.

Autopsy revealed a pyemic abscess in the myocardium with perforation of the anterior mitral leaflet. Pyemic abscesses were present also in the lungs, spleen, and kidneys.

Pathology described in cooperation with Dr. Albert J. Behar, of the Department of Pathology, Hebrew University Medical School.

P. O. Box 499.

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Mucormycosis of the Central Nervous System

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For many years Mucor and Rhizopus, class of Phycomycetes, have been considered purely saprophytic, but recently a number of cases of human infection by these organisms have been encountered. Fourteen cases [1-11] with involvement of the brain have been reported, and nine [2,3,7,9-11] of these had concomitant disease of the eyes. In each of these 14 cases the fungus infection complicated some other disorder, and all of the patients died of their fungal disease. In one other case the eye alone was involved and treatment by enucleation was successful.[12]

Paultauf [1] reported the first case with central nervous system involvement in 1885, but no other cases appear until 1943, when Gregory, Golden, and Haymaker [2] reported three new cases, all in middle-aged diabetics who were in diabetic coma when first seen. Subsequently LeCompte and Meissner,[3] Wolf and Cowen,[4] and Stratemeier [5] reported single cases, each in moribund diabetics. Baker and Severance [6] briefly report a case of nasal and brain involvement by fungus in a diabetic child. More recently Martin, Lukeman, Ranson, and Geppert [7] reported a case in a nondiabetic, but severely acidotic, infant. Kurrein [8] also reported a case in a uremic infant suffering from acute nephritis, and Gunson and Bowden [9] recorded a case in a child who had chronic glomerulonephritis.

Bauer, Ajello, Adams, and Useda Hernandez [10] reported two cases, each in a diabetic, with a culture productive of Rhizopus oryzae in one. Harris [11] recorded a case in a young diabetic in which Rhizopus arrhizus was cultured and in which recovery followed control of the diabetes, desensitization against the fungus, and administration of iodides. These last cases are the only ones in which the identity of the organism was definitely established by culture. Wadsworth [12] tells of a boy who presented as Coat's disease and whose enucleated eye contained fungi of the mucor species. The boy was healthy otherwise and remained so.

The case which I wish to present is that of a nondiabetic infant who showed a clinical picture which can be considered typical of cerebral and ocular mucormycosis, but whose disease was not diagnosed until histological preparations were made from material obtained at autopsy.

Report of Case

A 7-month-old boy was admitted to the University of Kansas Medical Center on Nov. 1, 1954. He had been well until one month before this, when he developed a severe gastrointestinal upset characterized by diarrhea and vomiting. Treatment with paregoric produced considerable relief, and his stools became formed. However, his fluid intake remained low, and he was markedly dehydrated when he was referred to this hospital seven days before death.

Physical examination at that time showed a dehydrated infant in shock. His right eye bulged, the lid was swollen, and the pupil did not react to light. The fundus was never clearly seen, although one observer thought that it appeared white. The left eye appeared normal. Respirations were rapid and coarse expiratory rhonchi were heard at the bases of the lungs. He had a marked tachycardia of 140-150 per minute. There was questionable nuchal rigidity, but no other abnormalities were noted.

Pertinent laboratory examinations at that time revealed a white blood cell count of 22,000 per cubic millimeter, with a normal differential. The CO_2-combining power was 4 mEq., the serum sodium was 167 mEq., the serum potassium 6.5 mEq., and the serum chloride 142 mEq.

Treatment with intravenous fluids, directed toward improving his hydration and correcting his

Submitted for publication Oct. 24, 1958.

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electrolyte imbalance was quite successful. Antibiotics, including penicillin, tetracycline (Achromycin) and chloramphenicol (Chloromycetin) were given, but his condition deteriorated rapidly. Three days before death a black necrotic area appeared on the nasal side of the right eye and he had prolonged periods of apnea, with muscular twitching. The necrotic area increased in size to involve the forehead and the bridge of the nose, and the adjacent tissue became edematous. His temperature fluctuated, but generally was elevated, and he had a persistent leukocytosis. Cultures of the right eye produced a scant growth of hemolytic Staphylococcus aureus. Two blood cultures and one spinal fluid culture were negative. However, three days before death his spinal fluid contained 371 white blood cells per cubic millimeter with 90% lymphocytes.

The infant died on Nov. 7, 1954.

Autopsy Findings

Gross.—The body was that of a well-developed, well-hydrated Negro child. There was edema of the soft tissue of the face and scalp, most marked on the right side, with conspicuous proptosis of the right eye. The skin of the inner margin of the right orbit, the bridge of the nose, and part of the forehead was black and gangrenous and the soft tissue of the orbit was soft and necrotic (Fig. 1). The right eye was extremely soft and had a cloudy anterior chamber so that the pupil was poorly visualized. It did not transilluminate, the vitreous was cloudy and the retina appeared necrotic.

Fig. 1.—Gangrene of orbit and nasal region.

The brain was extremely soft and mushy. Portions of it fell away when the dura was excised and only the pons and cerebellar hemispheres retained some semblance of normal shape and consistency. There was a great deal of fresh hemorrhage in both cerebral hemispheres, suggesting infarction, while a thin purulent exudate covered the meninges at the base of the brain and enclosed the vessels in this area. These vessels appeared to be thrombosed.

The ethmoid and the bones around the orbit were all soft and necrotic. The right cavernous sinus was filled with pasty, gray, putty-like material.

Apart from swelling and pallor of the kidneys and fatty changes of the liver the remaining organs were unremarkable.

Microscopic.—The striking features on microscopic examination were confined to the bones and soft tissues of the nose, paranasal sinuses, sella turcica and right orbit, and to the right eye, pituitary gland, and meninges covering the base of the brain, including the pons and cerebellum. In these areas there was extensive proliferation of large, broad, branching, nonseptate hyphae morphologically identical with those of the class of Phycomycetes, genus Mucor or Rhizopus (Fig. 2). These organisms showed a marked affinity for blood vessels, both arteries and veins being involved. Almost all of the vessels at the base of the brain were thrombosed, and there were masses of hyphae in their walls and lumens (Fig. 3). These thromboses caused almost complete infarction of both cerebral hemispheres while the necrosis of the skin of the nose appeared to be due to ischemia following occlusion of blood vessels in this area.

Many fungi lay free in the tissue, and here the reaction was mainly of an acute type, polymorphonuclear leukocytes being the predominant cell. This reaction was particularly intense in the meninges over the pons. No organisms were seen in either of the cerebral hemispheres.

The right eye was the site of an acute panophthalmitis, the major involvement being in the anterior portion. There was an acute inflammatory exudate in the anterior chamber that filled the angle of filtration. The exudate extended across the pupil and involved the iris and ciliary body as well as the cornea. Fungi were plentiful in this exudate. The vessels of the sclera were intensely congested, and many of them were plugged by thrombotic material and fungi. The retina was de-

Fig. 2. — Branching nonseptate hyphae from base of brain.

Fig. 3.—Thrombosis of vessel at base of brain with fungi in the wall and lumen.

tached, apparently because of the vascular occlusions rather than as a direct response to the inflammation. Hyphae were seen in the tissue supporting the optic nerve, but none could be found in the nerve itself. The nerve showed no degenerative changes.

No other organs were involved by the fungi, and the only other marked abnormality was in the kidneys, which showed an acute toxic nephrosis reflecting the severe septic process which was present in the eye and brain.

Comment

This case is typical of those previously described as "mucormycosis of the central nervous system," differing from the majority of cases principally in that there is no evidence that the child was a diabetic. The picture of acute ethmoiditis, ophthalmitis, and meningoencephalitis running a rapidly progressive course has been seen in almost all of the reported cases. At the time of autopsy a fungus was not suspected as the etiologic agent, and suitable cultures of the fresh material were not made. No growth was obtained on cultures made from frozen tissue. However, on a purely morphological basis there seems to be no doubt that one of the class of Phycomycetes was the responsible organism. Bauer and associates [10] isolated Rhizopus oryzae from a patient dying of cerebral mucormycosis, and Harris recovered Rhizopus arrhizus from another patient who survived. Otherwise none of the reported cases have productive cultures.

The belief that uncontrolled diabetes is a necessary factor for the development of Mucor infection of the central nervous system appears to be invalidated by this and the other recent cases reported.[7-9] Zimmerman [13] states that in reported cases of Mucor infection in the files of the Armed Forces Institute of Pathology diabetes has not been an impressive factor. He says that the disease has been seen most frequently as a complication of leukemia, carcinoma, multiple myeloma, burns, diarrhea, and antibiotic therapy.

Acidosis is the factor which virtually all of the reported cases of cerebral mucormycosis have in common. Carbon-dioxide-combining powers establishing this are available in some cases, and the clinical picture suggests that acidosis was present in the others.

Bauer, Flanagan, and Sheldon [14] found that alloxan diabetic rabbits inoculated intranasally with different strains of the Mucorales were susceptible to the development of cerebral mucormycosis, while control rabbits were not. It is not apparent why an organism so commonly found in nature should become so pathogenic in these individuals with disturbed metabolism. Antibiotic therapy cannot be incriminated in the case described since the infection was already well advanced before the patient was seen by a physician.

The route of infection in this case was through the nasopharynx into the right orbit and then to the base of the brain. The rapid death was due to the predilection of the organism for blood vessels, with resulting thrombosis and infarction.

Summary

This is the case of a 7-month-old child who developed a rapidly fatal infection caused by a fungus of the Phycomycetes class. This involved the ethmoid sinus, orbit, sella turcica, eye, and base of the brain with infarction necrosis of both cerebral hemispheres. The child was not a diabetic, but was in a severe state of acidosis following an intestinal upset. Acidosis appears to be a factor which permits this ordinarily harmless organism to become pathogenic. In spite of the typical history and physical findings, the disease was not recognized either clinically or at autopsy until histological preparations were examined.

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Congenital Prepyloric Gastric Atresia

A Report of Two Cases

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Congenital atresias of the pylorus or stomach are rare compared with complete obstructions elsewhere in the intestinal tract. A thorough review of the literature revealed seven previously reported case histories of patients in whom this diagnosis was made clinically or at autopsy. We have successfully treated two premature infants with prepyloric gastric mucosal atresia at Children's Hospital of Michigan. We would like to add their histories, along with a summary of our review, to the literature.

Types of Obstruction and Review of the Literature

Pyloric and gastric obstruction of the newborn can be divided into two general groups: complete and incomplete. The latter condition is common owing to the incidence of pyloric stenosis, which does not usually cause symptoms until the patient is 2 or more weeks of age. Another type of incomplete occlusion of the gastric canal is the result of obstruction by an intrinsic mass of the gastric wall. Lyon,[1] Bikoff,[2] and others have reported cysts of the gastric wall which, upon filling, occluded the gastric or pyloric lumen. These cysts were formed by aberrant gastric mucosa or pancreatic tissue. The nine patients with complete pyloric or gastric obstruction, including the two presented in this paper, can be divided into three groups on the basis of the anatomical findings: (1) obstruction due to single or double diaphragms, (2) an area of mucosal atresia, and (3) complete seg-

Received for publication July 2, 1958.

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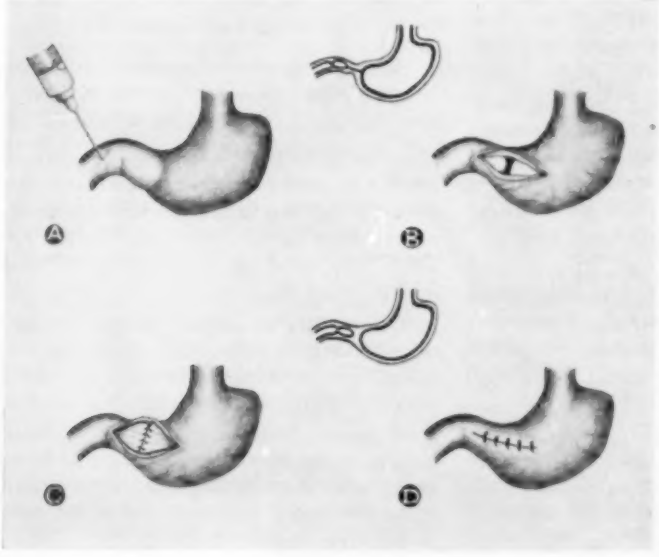


Fig. 1.—The diagrammatic illustrations show the two types of prepyloric gastric mucosal atresia encountered in the patients reported. The upper diagram illustrates the existence of a cord of tissue connecting the proximal and distal mucosal pouches, which was not demonstrated in the second patient represented by the lower diagram. *A*, the proximal duodenum was distended by injecting isotonic saline solution to locate the point of obstruction. *B*, a seromuscular incision revealed the mucosal pouches. *C*, after transverse incisions into the mucosal pouches, the margins were approximated by an end-to-end anastomosis. *D*, the seromuscular layers were then closed by interrupted sutures.

mental aplasia of the gastrointestinal tract (Fig. 1).

In 1937, R. J. Bennett Jr.,[3] reported a patient with a pyloric diaphragm mistakenly diagnosed as pyloric stenosis. A Ramstedt procedure was performed, but the patient died 36 hours later, and autopsy revealed a thin diaphragm in the pyloric canal. Touroff and Sussman[4] reported, in 1940, a patient in whom gastrotomy revealed a prepyloric membrane which was perforated surgically, after which the patient made a good recovery. A third patient reported by Benson and Coury,[5] in 1951, was operated upon on the sixth day of life with excision of the diaphragm. There was persistent vomiting postoperatively, which was thought to be due to edema at the operative site. A gastrojejunostomy was performed on the 27th day, and the patient did well thereafter.

Metz, Householder, and DePree,[6] in 1940, reported the case history of a patient who had a double prepyloric membrane resulting in a cyst-like structure between the two membranes. Surgery was performed on the 3d day of life with incision of the diaphragms, and the patient had no further difficulty. In 1942, Berman and Ballenger[7] reported an interesting history of a 2-year-old boy with symptoms of high intestinal obstruction. Exploratory gastrotomy revealed a prepyloric membrane with a 2 mm. diameter central opening. The diaphragm was incised, with consequent disappearance of the symptoms. Further review of the literature revealed seven other cases of a similar diaphragm with a small orifice. These did not become symptomatic until adult life, ages 35 to 74 years, and were treated surgically at that time.[8-13] One other child has come to our attention with a roentgenographic diagnosis of partial prepyloric membrane; symptoms to date have not necessitated surgery.[14] These 13 reported cases represent complete or partial pyloric or prepyloric obstruction due to persistence of mucosal diaphragms.

We found one instance of aplasia which was reported by Holladay[15] in 1946. Surgery was performed on the seventh day of life and a 2 cm. area of pyloric aplasia was present. A gastrojejunostomy was performed, but the patient died on the fourth postoperative day with autopsy evidence of pneumonitis and peritonitis.

In 1947, Burnett and Halpert[16] reported the history of a patient with pyloric atresia. On the second day the patient showed symptoms of perforation of a hollow intra-abdominal viscus. At surgery a gastric perforation was sutured, but the patient died the following day. Autopsy revealed an area of minimal pyloric narrowing for a length of about 1 cm. When the serosa was opened at this point, an absence of muscularis and mucosa was demonstrated, and the segment was filled with loose, vascular connective tissue like that of the submucosa. Fell[17] reported a patient with pyloric atresia in 1951, in discussion of the paper by Benson and Coury. A diagnosis of high obstruction was confirmed by roentgenogram, and exploratory laparotomy on the 12th day revealed an area of atresia at the pylorus. An anterior gastroenterostomy was performed, but the patient died five days later with evidence at autopsy of bronchopneumonia and perforation at the site of anastomosis.

Report of Cases

The histories of these two patients with prepyloric gastric mucosal atresia present a few similarities which probably are of no more than coincidental significance. It is of interest to note that each mother had delivered a stillborn infant prior to this pregnancy. Both mothers had renal disease for which they were being treated at the time of delivery of these patients. Both delivered premature infants (one weighed 3 lb. 5½ oz. [1,515 gm.]; the other 3 lb. 8½ oz. [1,600 gm.]) at approximately the same period of gestation, with identical anomalies. Both infants had lost 30% of their birth weight by the time they were operated on, and it was 12 to 14 days after birth before either received a significant amount of fluid or nutrition orally.

CASE 1.—A premature, female Negro infant was admitted to Children's Hospital at the age of 9 days on Oct. 24, 1956. The child was born Oct. 15, 1956, of an 18-year-old Negro who was Gravida 2, Para 0. The mother's previous pregnancy terminated at three months in a spontaneous abortion. She received penicillin therapy from March through September, 1956, "for her blood," and her serology was positive at the time of delivery. In the month prior to this delivery, the mother developed back pain which was diagnosed and treated as renal disease. On Oct. 15, 1956, after spontaneous rupture of the amniotic membranes, a female child weighing 3 lb. 5½ oz. (1,515 gm.) was delivered.

The infant responded immediately after delivery, but when 3 hours old began to have respiratory distress because of unusually copious amounts of mucus in the oropharynx. Glucose water gavage feedings were begun 24 to 36 hours after birth, but all of these feedings were regurgitated by the infant. Episodes of cyanosis apparently due to the aspiration of mucus continued. The patient was then given subcutaneous plasma and fluids until the sixth day of life. Bowel movements were recorded on the chart at 6 hours, 36 hours, 6 days, and 7 days. Formula feedings were begun on the sixth day, but again all feedings were regurgitated, and parenteral fluids were continued. On the ninth day, epigastric distention was noted, and the patient was transferred to Children's Hospital of Michigan.

Physical examination at the time of admission revealed the patient to be a small, dehydrated female infant with scanty subcutaneous tissue and a marked loss of turgor. There was no abdominal distention. The weight at this time was 2 lb. 7 oz. (1,115 gm.). Roentgenograms of the patient's chest and abdomen that evening revealed normal intrathoracic structures and abdominal gas which was limited to the stomach. Gavage feedings were attempted, but again resulted in regurgitation and cyanosis. The following day a roentgenogram of the abdomen was repeated, and, as previously demonstrated, there was gas only in the stomach. With this evidence of high gastrointestinal obstruction, surgical exploration was indicated.

Operative Report.—Under general endotracheal anesthesia, a left paramedian incision was made. The duodenal bulb was elevated, and examination revealed "virginal" intestine, both small and large. Isotonic saline, 10 cc., was injected into the duodenum with a syringe and needle. This passed readily down the jejunum, demonstrating the absence of obstruction beyond this point. There was apparent enlargement of the pylorus, with slight narrowing of the antrum proximal to it, suggestive of a pyloric stenosis. The pyloric serosa and muscularis were incised longitudinally down to the mucosa, which pouched up in a normal fashion. At the proximal end of the incision the mucosa seemed to narrow, so the incision was extended along the antrum of the stomach. This revealed the mucosa narrowing down to a small cord. The cord was about ¼ in. in length, proximal to which it again ballooned out into the gastric mucosal pouch. Upon transection of this segment there was no demonstrable lumen. The cord was excised, and a transverse incision was made across the ends of both the proximal and distal mucosal pouches. These were anastomosed over a rubber-tipped polyethylene tube which had been passed through the anastomosis via the upper gastrointestinal tract. The muscularis and serosa were closed transversely over the mucosal anastomosis. The duration of the operation was one hour, during which the patient received 55 cc. of whole blood (equal to 50% of her blood volume) to replace the estimated loss. The patient's temperature had dropped to less than 92 F despite the use of a heating pad.

In the postoperative period the child was maintained by subcutaneous fluids for the next day and a half, after which feedings of glucose water were administered through the gastroduodenal tube. Two consecutive feedings were regurgitated, so feedings were discontinued. On the third postoperative day tube feedings were begun. These feedings were retained. By the sixth postoperative day she was taking 15 cc. of full-strength premature stock formula and weighed 2 lb. 9 oz. (1,160 gm.). The gastroduodenal tube was removed on the 10th postoperative day. Thereafter, until discharge, daily increments in formula, occasionally supplemented with fluids by parenteral routes, resulted in a slow but progressive weight gain. She was discharged 10 weeks after operation weighing 4 lb. 14 oz. (2,210 gm.) and taking up to 3 oz. per feeding. When last seen in the clinic on Sept. 25, 1957, her weight was 18 lb. 8 oz. (8,390 gm.); she was 11 months old and had continued to do well. She was then eating puréed meats and vegetables in addition to adequate amounts of formula.

CASE 2.—A white, male premature infant was admitted to Children's Hospital on Jan. 29, 1957, at 6 days of age. The child was delivered by a 31-year-old white woman, who had been hospitalized for eight weeks prior to delivery because of a symptomatic right hydronephrosis. The mother had a stillborn child in March, 1956, after six months gestation. There is one other sibling alive and well at 6 years of age.

The infant was delivered on Jan. 14, 1957, and cried readily after its oropharynx was aspirated. His birth weight was 3 lb. 8½ oz. (1,600 gm.). He was placed in an Isolette until the initial gavage feedings were started, approximately 36 hours after birth. The patient started to vomit and

became cyanotic after the second feeding. Aspiration of the oropharynx was performed and caffeine and sodium benzoate was administered intramuscularly to the infant during this phase. He was fed by gavage at irregular intervals with similar results until transferred to Children's Hospital. Prior to admission the patient had passed one normal-appearing meconium stool, the only recorded stool in the first six days of life.

On admission to Children's Hospital the child weighed 2 lb. 9½ oz. (1,175 gm.). Physical examination revealed a strong and active, moderately dehydrated, jaundiced premature infant. The skin was lightly icteric. The other positive finding was the scaphoid abdomen with slight fullness in the epigastric region. Roentgenograms of the abdomen were made in the supine and upright positions on the day of admission and repeated on the day following admission. These revealed an air- and fluid-filled structure in the left upper quadrant. There was no gas or fluid demonstrated elsewhere in the abdomen except a few small gas bubbles in the rectum, the result of rectal examination and insertion of the thermometer.

The history and roentgen findings indicated the presence of a complete high intestinal obstruction, probably a prepyloric gastric atresia. The day following admission the infant was operated upon under general endotracheal anesthesia. At this time he weighed 2 lb. 9 oz. (1,162 gm.).

Operative Procedure.—The abdomen was explored via a right paramedian rectus retracting incision. The stomach was distended; the duodenum and a small bowel were of small caliber and free of gas or fluid, with the appearance of "virginal" gut. Approximately 10 cc. of isotonic saline was injected into the first portion of the duodenum and the fluid appeared to go "both ways." The fluid distended the duodenum and jejunum distally and also the first portion of the duodenum through the pylorus, as designated by the pyloric vein, and into the prepyloric area of the stomach. It *did not* inflate the antral portion of the stomach. An incision was made in the pyloric area longitudinal to the axis of the bowel in the manner of a Ramstedt pyloromyotomy. The fibers of the muscularis of the pyloris and antral end of the stomach were separated, making it possible to visualize the pouting mucosa of the pylorus. It terminated in a "blind" pouch and was separated from the pouched portion of the gastric mucosa by several millimeters. The antral mucosa and the pyloric mucosa were opened, and the two mucosal pouches brought together in a one-layer end-to-end anastomosis. Before completion of the anastomosis, a nasogastric catheter was inserted and advanced through the anastomosis into the proximal duodenum. The muscularis and serosal layers of the stomach and duodenum were approximated in a longitudinal closure. The patient withstood the operative procedure well, although his body temperature was too low to register on a 92-degree Fahrenheit clinical thermometer.

The child's immediate postoperative course was essentially uneventful, and 48 hours after surgery glucose feedings were started via the duodenal tube. Such feedings were continued and gradually increased until the fourth postoperative day, at which time oral feedings of glucose water were started. One week after surgery, the child was started on premature stock formula, with daily increments. The child's postoperative course was then complicated by a persistent superficial wound infection from which a heavy growth of hemolytic Staphylococcus aureus coagulase positive was cultured. Chloramphenicol was administered orally. This antibiotic controlled the infection successfully so long as the child received the medication. Vomiting, which occurred approximately one month after the surgery, prompted an upper gastrointestinal barium study. This revealed some difficulty in the child's ability to swallow the barium. Once the barium was in the stomach, it passed readily into the small bowel. The child's course continued to be one of slow but progressive weight gain, delayed only by exacerbations of the wound infection when the antibiotic was temporarily discontinued. He was discharged on the 73d hospital day, weighing 5 lb. 3 oz. (2,355 gm.). At this time the wound was well healed.

A check-up examination approximately seven months from the surgery indicated the child to be well and robust, weighing 12 lb. 4 oz. (5,555 gm.). The child was eating four to five jars of baby food, and cereal in addition to 30 oz. of formula daily.

Comment

The absence of the cardinal signs of intestinal obstruction in a newborn may, in part, explain the rarity of reported patients with prepyloric gastric atresia. These infants *do not* have the "bile-stained" vomiting, abdominal distention, or absence of meconium stools which typically sound the alarm. Their symptoms are predominantly respiratory. The child may appear to have "excessive salivation," but a check for esophageal atresia finds the catheter passed readily into the stomach. The stomach is "full" at birth, and the "overflow" mechanism of aspiration of esophageal contents is similar to that seen in infants with esophageal atresia. In the absence of distention of the abdomen, the absence of bile

in the stomach, and a relatively normal-appearing meconium stool soon after birth, the intestinal tract is regarded as being patent. Vomiting will occur at variable intervals after feeding—but cough, dyspnea, and cyanosis are the more distressing features of the episodes. Since these children may be born prematurely, the symptom complex could be attributed to immaturity of neuromuscular control or intracranial birth injury. Thereafter, the diagnosis of gastric atresia reasonably soon after birth depends upon the knowledge that such an anomaly does occur and may be manifest by respiratory distress. Having enough suspicion to follow up with roentgen examination of a clinically normal-appearing abdomen and gastrointestinal tract in such patients would be rewarding (Figs. 2 and 3).

The syndrome of prepyloric gastric atresia is characterized by (1) vomiting and respiratory distress, which is persistent despite various feeding techniques and formulas; (2) development of epigastric distention, with the remainder of the abdomen scaphoid; (3) stools fewer initially and decreasing in number until absent; (4) roentgenographic studies revealing air and gas in the abdominal cavity limited to the stomach.

It is of interest to note that in spite of 30% weight loss and no enteral feedings until the infants were 12 to 14 days old, they survived. The principles of pre- and

Fig. 2.—The admission roentgenogram reveals the gas and fluid in the abdomen to be limited entirely to the stomach. The abdomen is unusually small.

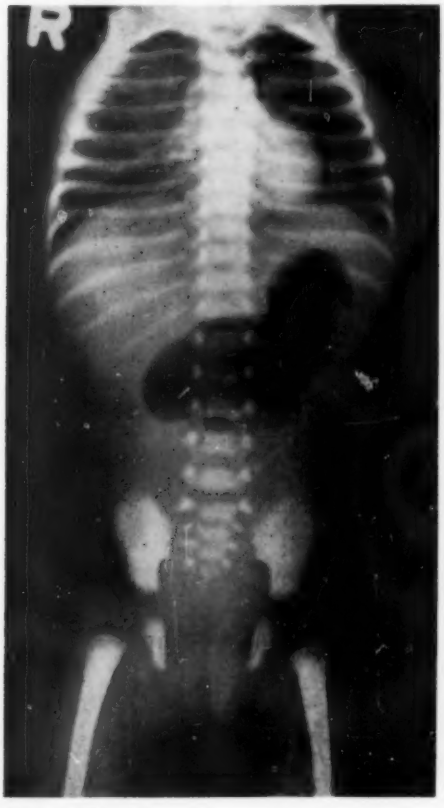
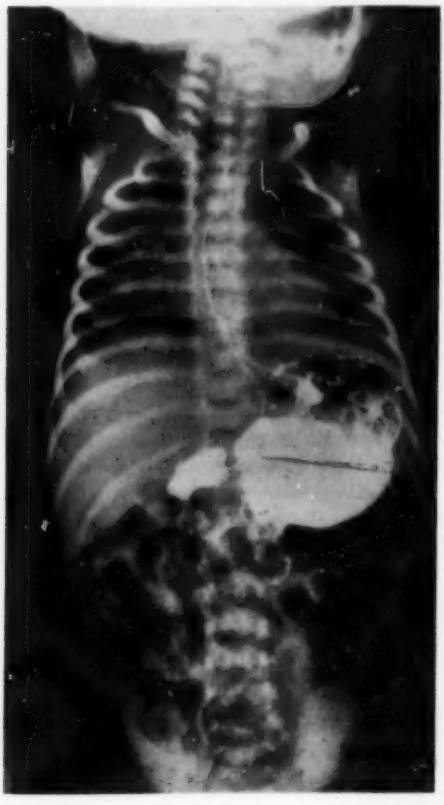


Fig. 3.—An upper gastrointestinal study prior to discharge revealed a widely patent prepyloric canal.



postoperative and surgical management resulting in success with these reported patients were those generally utilized in care of the newborn and premature infant with intestinal atresia. Such care is dependent upon complete cooperation and understanding of the problems peculiar to these patients by the pediatrician, nursing personnel, surgeon, and anesthetist.

Summary and Conclusion

Complete congenital atresia of the pyloric or gastric canal is a rare anomaly. We were successful in finding only seven patients with this condition who had been previously reported in the world literature.

The types of obstruction encountered are (*a*) single or double diaphragm (four cases), (*b*) atresia (two cases), and (*c*) aplasia (one case).

The two successfully treated patients with prepyloric gastric atresia reported in this paper were premature infants weighing less than 3 lb. (1,360 gm.) at the time of operation.

Proper diagnosis of this anomaly depends upon the knowledge that such a condition may exist. The earliest signs are vomiting, respiratory distress, epigastric distention, fewer to absent stools, and roentgenographic finding of abdominal gas and fluid limited to the stomach.

In both infants, a direct end-to-end anastomosis was utilized to correct the atresia.

The problems of management and care of such small surgical patients are those of care of the premature infants in general.

The drawings were prepared by Dr. Ruth Campbell.

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Clinical Notes

A New Ceruminolytic for Use in Pediatric Ear Examinations

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Some degree of involvement of the middle ear is present in practically all upper respiratory infections of infants and small children.[1] It therefore becomes evident that an adequate examination of the tympanic membrane and ear canal is of primary importance in pediatrics. Statistical studies have shown that over 30% of ears in which disease is present may have the tympanic membrane totally obscured by wax.[2]

The removal of ear wax in a sick child who is suffering not unusually from a fair degree of pain is a difficult problem. Removal of wax with a blunt curette is safe only if the child is cooperative, which is rarely the case. Irrigation with warm water is a lengthy and inconvenient procedure, which must be done with great caution in young children since only a little pressure may be enough to rupture an inflamed tympanic membrane. Also, in this procedure, cooperation is important, and this is rarely forthcoming. Hydrogen peroxide irrigation may also be used, but usually must be repeated at fairly long intervals to successfully clean the ear canal. Because of the difficulty in removing ear wax simply and efficiently, it has often been necessary to defer ear examination for some time until the canal can be cleaned, certainly an inadvisable thing to do in an acutely ill child.

We have been using for some time a new ceruminolytic agent, Cerumenex,* to assure proper examination of the ears of our pediatric patients. This material, a yellow nonirritating liquid, depends for its action on a triethanolamine polypeptide oleate condensate, which is capable of forming a chelate complex with the protein content of cerumen. Since dried ear wax contains 60% protein, this action results in loosening the wax plugs and softening and sludging of the wax itself.

Our procedure was to examine the ears at the beginning of the physical examination. When large amounts of cerumen interfering with proper visualization of the drum were noted, the ear canal was approximately half-filled with Cerumenex and the external auditory meatus plugged with a cotton plug. At the end of the examination, some 10 to 15 minutes later, one of two procedures was carried out.

When children were examined in the home, where an ear syringe was usually not on hand, a cotton swab was gently inserted into the ear canal and the canal wiped with a rotating motion. In 20 children with occluded ear canals, it was possible to visualize the tympanic membrane with this procedure in 15. In the other five, the canal was again filled with Cerumenex, which was permitted to remain overnight. The next morning, removal of the cotton plug was followed by the appearance of a brownish liquid material; the canal was found to be clear, and the tympanic membrane was easily visible.

When children were examined in the office, the application of Cerumenex for 15 minutes was followed by the use of a very gentle warm water irrigation, using only a total volume of 20 cc. Out of 20 cases so treated, the tympanic membranes of 19 were rendered clearly visible. In the 20th a repeated treatment with Cerumenex and a second 20 cc. of warm water syringing resulted in successful clearing of the canal.

For purposes of comparison, two groups of 20 children were treated in a similar manner with use of hydrogen peroxide instead of Cerumenex.

In the first group, treated at home by filling the ear canal half-full of hydrogen peroxide and swabbing with a cotton swab 15 minutes later, it was possible to visualize the tympanic membrane in six, with a single application. With overnight use of peroxide, it was possible to visualize another six canals. The remaining eight remained occluded.

The second group was treated with hydrogen peroxide for 15 minutes and then by gentle irrigation. Here it was possible to clear 10 of the 20

Comparative Results with Cerumenex and Hydrogen Peroxide

Home Treatment Medication & Swab % Successfully Treated		Office Treatment Medication & Irrigation with 20 cc. of Warm Water % Successfully Treated	
Cerumenex	Peroxide	Cerumenex	Peroxide
75	33	95	50
After Second Treatment			
25	33	5	0

Submitted for publication July 2, 1958.

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* Cerumenex, distributed by the Purdue Frederick Company, New York.

canals so that the tympanic membrane was well visualized. The comparative results are summarized in the Table.

Five cases in the first Cerumenex group and three in the second were diagnosed as otitis media, acute, catarrhal, when the tympanic membrane was visualized. In all of these cases, the wax was removed on the first try. None of these children complained of any discomfort during the procedure, and two, who were in considerable pain at the time, tolerated the procedure quite well, and did not complain of any additional discomfort.

All of the above children were reexamined 24 hours after the original wax was removed for evidence of irritant action by the Cerumenex. The ear canals appeared normal in all cases, and the eight cases with otitis media appeared to be following the expected course for this condition.

The use of an effective ceruminolytic, Cerumenex, appears to be a valuable adjunct in pediatric examination where visualization of the tympanic membrane is of prime importance. It facilitates early diagnosis and treatment of otitis media and obviates the occasional omission or deferment of a part of the physical examination which is essential.

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Pseudo Pectus Excavatum in the Newborn Due to Lower Respiratory Tract Disease

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Pectus excavatum or funnel chest is one of the most obvious deformities of the chest. It is usually congenital in origin, but it may be associated with respiratory tract obstruction or rickets.[1]

Lester [2] has observed an acquired funneling of the lower sternum which occurs in the newborn infant after the onset of lower respiratory tract disease. He has called this condition pseudo pectus excavatum.

The purpose of this communication is to report our observation of nine newborn infants who had normal anterior chest walls at birth, all of whom suffered respiratory distress and developed pectus excavatum shortly after the onset of dyspnea.

Clinical Observations

On the nursery services of two large general hospitals 4,216 consecutive infants were observed; 451 (10.7%) were premature (Table 1).

None of the infants had thoracic cage abnormalities at birth. Obvious lower sternal depression was present, however, in nine infants, seven of whom were premature, by the age of 3 days. Each of these babies had experienced respiratory distress prior to the appearance of the deformity (Figs. 1 and 2).

Two infants did not survive. One died at 36 hours of life; the other died 12 days after birth.

TABLE 1.—*Incidence of Pseudo Pectus Excavatum*

	Infants Observed	Infants Who Developed Pseudo Pectus Excavatum
Term	3,765 (89.3%)	2 (0.05%)
Premature	451 (10.7%)	7 (1.55%)
Total	4,216 (100%)	9 (0.21%)

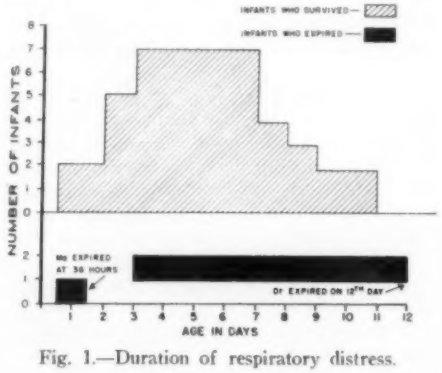

Fig. 1.—Duration of respiratory distress.

Submitted for publication Sept. 9, 1958.

From the Departments of Pediatrics, University of Maryland School of Medicine, The University of Maryland Hospital, and the Lutheran Hospital of Maryland.

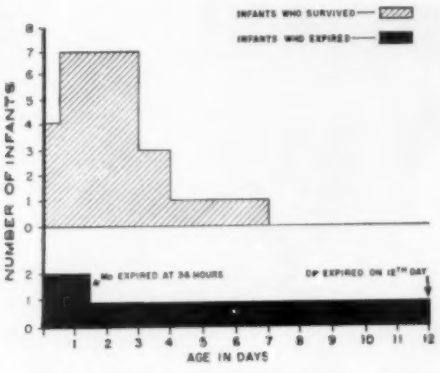

Fig. 2.—Duration of pectus excavatum.

Both of these babies had respiratory distress until the time of death, and both had marked funneling of the lower sternum when they died (Table 2). In each of the seven infants who survived, the anterior chest wall had returned to normal after cessation of respiratory distress. Each had normal contour of the thoracic cage by the 11th day of life.

Slight sternal depression was first noted in each infant in the midline, usually at the level of the third or fourth rib. As the respiratory distress continued, the depression became deeper and extended caudad to form a V-shaped deformity extending beyond the midclavicular line. Figure 3 shows the sequence of events of the anterior chest wall of one of the infants (Case 8), beginning with the early formation of funnel chest on the day of birth (Fig. 3*A*), progressing through marked sternal depression on the fourth day of life (Fig. 3*B* and *C*) and returning to normal by 9 days of age (Fig. 3*D*).

Clinical diagnosis of pulmonary hyaline-membrane disease was made in seven infants; one had pneumonia, and another had pneumonia and sclerema. Postmortem findings of the two infants who died confirmed the diagnosis of pneumonia in one baby and pulmonary hyaline-membrane disease in the other.

Four infants had abnormal respirations from birth; all were in respiratory distress by 12 hours of life. The mean age of onset was 3.0 hours.

Chest wall deformities were noted as early as 8 hours of life and as soon as four hours after the onset of dyspnea. In all infants, funneling of the sternum was present by the third day of life. The average age at appearance of sternal depression was 45 hours.

Of those infants who survived, respiratory distress persisted for 3 days in four babies, for 4 days in two, and for 7 days in the other (mean, 3.1 days).

The anterior chest wall returned to normal by the 11th day of life in all infants who survived. Three infants had normal chest walls by the 7th day of life, one on the 8th day, one on the 9th day, and two on the 11th day of life. The mean age of return of the chest wall to normal was 8.6 days.

Comment

Changes in lung function can alter the shape of the thoracic cage, as, for example, in emphysema. This is true in children and adults as well. Since the bony structures of the newborn are incompletely calcified and since the nonosseous structures are soft, spongy, and less rigid at this age, it is not surprising that chest wall deformities occur with prolonged dyspnea.

Normal respiratory effort in the newborn is principally performed by the piston-like action of the diaphragm.[3] The costosternal fibers of this muscle arise from the posterior aspect of the xyphoid and from the cartilage and adjacent portions of the six

TABLE 2.—*Time Relation Between Onset and Duration of Respiratory Distress and Pseudo Pectus Excavatum*

Case	Sex	Race	Birth Weight, Gm.	Age at Onset of Dyspnea, Hr.	Age Dyspnea Subsided, Days	Age Depression of Sternum Noted, Days	Age Depression of Sternum Corrected, Days	Diagnosis
1	M	W	2,580	2	3	3	8	Pulmonary hyaline-membrane disease
2	F	W	1,475	Birth	3	2	7	Pulmonary hyaline-membrane disease
3	M	W	2,355	Birth	3	2	7	Pneumonia (congenital)
4	F	W	2,465	Birth	3	10 hr.	7	Pulmonary hyaline-membrane disease
5	M	W	3,940	3	4	3	11	Pulmonary hyaline-membrane disease
6	M	N	1,020	Birth	Died on 12th day	3	Present at death	Pneumonia, sclerema
7	F	N	1,475	12	7	2	11	Pulmonary hyaline-membrane disease
8	F	W	1,840	6	4	12 hr.	9	Pulmonary hyaline-membrane disease
9	F	N	1,360	4	Died at 36 hr.	8 hr.	Present at death	Pulmonary hyaline-membrane disease

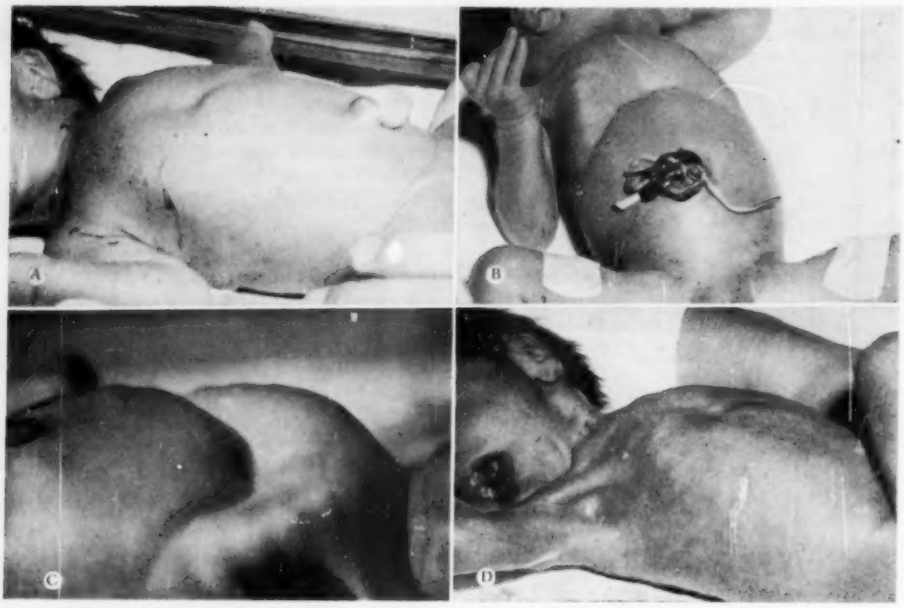

Fig. 3 (Case 8).—*A*, at the age of 17 hours. Dyspnea began at 4 hours of life. Sternal depression is beginning. *B*, on the fourth day of life. The sternal depression is more marked; the thorax is barrel-shaped. *C*, close-up view on same day. *D*, at age 9 days the chest wall has regained normal contour.

lower ribs. The diaphragm contracts during inspiration, and the lower ribs are drawn inward.

The inspiratory decrease of intrapleural pressure in the diaphragmatic region of the thorax is considerably greater than in the apex or other parts of the lung.[4] Harrison's groove is an example of deformity which may develop if the structures are soft and yielding.

When abnormal pulmonary functions supervene, the accessory muscles of respiration are utilized; the ribs and intercostal muscles perform a more active function in implementing the respiratory excursion.

The floating ribs (11th and 12th), having no attachment to the sternum, do not contribute directly to sternal position during respiration. The upper 10 pairs of ribs are attached to the sternum. The ribs from the 7th to the 10th swing upward and outward on inspiration.[6] Because of the action of the external intercostal muscles, each of these ribs rotates around an oblique anteroposterior axis which passes through the midline in front and the rib neck behind (Fig. 4). As a result, the distance between the vertebral column and the sternum is actually decreased when the lungs expand. This combination of forces, the inward pulling of the diaphragm plus the action of the external intercostal muscles, tend to produce depression of the lower anterior chest wall.

The upper ribs also move upward and outward during inspiration. However, the upper sternum is thrust forward and outward (Fig. 5) and the

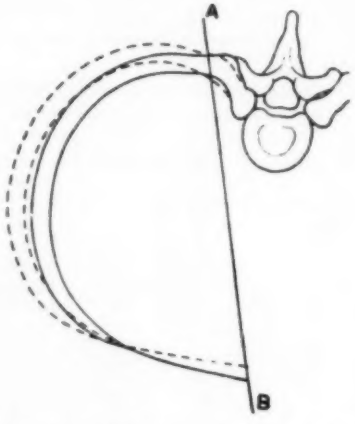

Fig. 4.—The axis of movement (*AB*) of a vertebrochondral rib (7th to 10th ribs). The interrupted lines indicate the position of the rib in inspiration. Reproduced from Gray, H.: Anatomy of the Human Body, Ed. 26, edited by C. H. Goss, Philadelphia, 1954, courtesy of Lea & Febiger, Publishers.

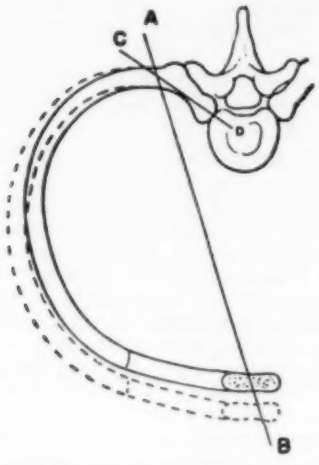

Fig. 5.—The axes of movement (*AB* and *CD*) of a vertebrosternal rib (second to sixth ribs). The interrupted lines indicate the position of the rib in inspiration. Reproduced from Gray, H.: Anatomy of the Human Body, Ed. 26, edited by C. H. Goss, Philadelphia, 1954, courtesy of Lea & Febiger, Publishers.

anteroposterior diameter of the thorax is increased, producing the so-called barrel chest.

Thus, the distance between the vertebral column and sternum is increased in the superior aspects of the chest, while this distance is decreased in the inferior aspects, as a result of the respiratory effort. This phenomenon is demonstrated in Figure 3*C*.

Congenital pectus excavatum is present at birth or develops shortly thereafter. It may become more marked as the person grows and shows no tendency to spontaneous cure. Surgery has been recommended in severe cases.

Little difficulty should be experienced in differentiating the congenital type from pseudo pectus excavatum (Table 3). The acquired form is never present at birth. Respiratory distress precedes its appearance in all cases, resulting in definite changes in the contour of the anterior chest wall by the age of 3 days. If the infant survives, spontaneous improvement follows shortly after improvement of respiratory distress.

In pseudo pectus excavatum it is important to recognize that depression of the sternum is the result of dyspnea and not the cause of it.

TABLE 3.—*Pectus Excavatum*

	Congenital	Pseudo
Present at birth	±	−
Definite changes in first 3 days of life	−	+
Respiratory distress precedes appearance	−	+
Spontaneous improvement	−	+
Commoner in prematures	−	+
Upper thorax barrel-shaped	−	±

Summary

In a series of 4,216 consecutive newborn infants, 9 developed depression of the lower portion of the sternum after the onset of respiratory distress. Seven of the infants were premature.

Two of the babies died; both had respiratory distress and funneling of the lower sternum at the time of death. The anterior chest wall returned to normal by the 11th day in all the infants who survived.

A brief discussion is presented of the mechanism whereby the anteroposterior diameter of the superior portion of the thorax could be increased and simultaneously the same measurement in the inferior portion decreased, as a result of the same process.

It is pointed out that in pseudo pectus excavatum depression of the sternum is the result of dyspnea and not the cause of it.

University of Maryland School of Medicine (1).

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Improvised Infant Proctoscope

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Occasions demanding the use of an infant proctoscope are so infrequent in a small hospital that the expense of such equipment is sometimes not justified. Occasionally, however, a simple problem will arise which can be solved by makeshift equipment. This will obviate the necessity of transporting the patient to a more elaborately equipped facility.

Submitted for publication Oct. 15, 1958.

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Fig. 1.—Improvised infant proctoscope.

Most pediatricians know of the usefulness of a test tube inserted into the anal orifice for visualization of anal and lower rectal pathology. Recently we had occasion to modify an otoscope for use in the same way, with the added advantage that limited manipulation could be carried out.

An otoscope with a diagnostic head and nasal speculum is most suitable for this purpose. An appropriate length of plastic or rubber tubing (2 in. for the lower rectum) is slipped over the end of the nasal speculum. A piece cut from a large catheter or a plastic rectal tube can be used here. If plastic tubing is used, it should be heated with

Fig. 3.—Proctoscope in use.

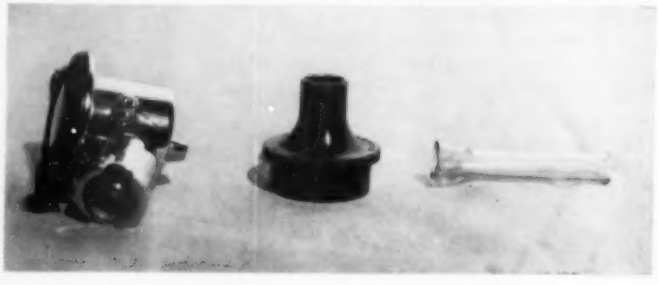

Fig. 2.—Component parts of proctoscope.

hot water and stretched onto the speculum with a hemostat. The cut edge can be smoothed with an open flame.

With use of surgical lubricant, the end of the tubing is inserted into the anal orifice with the infant in a knee-chest position. The otoscope light is turned on, and under direct vision the instrument can be inserted to the hilt of the nasal speculum. The examiner must take care to keep the tubing in a straight line to gain an optimum field of vision. Also one must keep in mind the relatively straight vertical orientation of the infant's rectum.

The procedure described is simple, rapid, and free of trauma to the infant. Within limitations it is useful in locating and removing foreign bodies in the lower rectum, and in identifying minor pathology in this area.

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Neonatal Transanal Perforation of the Rectum

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Accidental transanal perforation of the rectum in the newborn infant has been reported only once. This report of the second fatal case is to call attention to this neonatal hazard, awareness of which may permit early diagnosis and treatment of the resulting peritonitis.

Report of a Case

The patient, a white boy, was the product of a nine-month uncomplicated pregnancy and uneventful delivery. He appeared normal in all respects and so received routine newborn care, which included the rectal measurement of the temperature upon admission to the nursery and once daily. His color, activity, stools, and feedings were normal until early on the fourth day, when he seemed sleepy and anorexic and he was slightly jaundiced with occasional tachypnea. Later that day he became lethargic, with sunken eyes, a weak feeble cry, abdominal distension, reduced motor activity and distinct jaundice. In addition, a trace of bloody mucus was found on the rectal examination. The blood appeared to be from a small anterior anal tear.

A diagnosis of septicemia was made, and treatment was begun with intravenous sulfisoxazole and penicillin and intramuscular chloramphenicol. Hemoglobin was 15.8 gm. The white blood count was 2,050 cells per cubic millimeter with a differential of 26 neutrophils, 70 lymphocytes, and 4 monocytes. The total van den Bergh reaction was 10.2 mg. %. Spinal fluid had no cells, 43 mg. % sugar, and 44 mg. % total protein. Cerebral spinal fluid culture was sterile, but a blood culture obtained from the jugular vein was positive for Escherichia coli. Roentgenograms of the chest and abdomen were read as normal.

Submitted for publication Oct. 17, 1958.

His condition became worse gradually, although his white blood count returned to normal over the next two days. On the sixth day he had convulsive movements of his arms and legs, which were controlled with phenobarbital and diphenylhydantoin sodium. These occurred with an isolated temperature elevation of 103.2 F. He died early on the seventh day after developing sclerema neonatorum. A postmortem blood culture was sterile.

Autopsy Findings.—The significant findings were limited to the abdomen. There was a severe fibrinopurulent peritonitis with accumulations of exudate in the rectovesical pouch and in the right and left upper quadrants of the abdominal cavity. A perforation 2 to 3 mm. in diameter was identified in the anterior wall of the rectum immediately beneath the inferior rectal fold. The perforation was 2 cm. proximal to the anus and communicated with the rectovesical pouch, where a yellow-gray exudate with small fragments of yellow material resembling a milk stool was adherent to the peritoneum. Microscopic examination of representative sections through the perforated area revealed recent hemorrhage into the connective tissue between the seminal vesical and the anterior rectal wall and into the muscularis of the rectum. The exudate was of the fibrinopurulent variety with enmeshed desquamated epidermal cells. Exudate from the upper abdominal cavity had a similar appearance microscopically. There was no gross or microscopic evidence of a congenital defect in the muscularis of the rectum.

Comment

The autopsy findings suggest that a transanal perforation of the rectum caused the peritonitis. In this case, as in the case reported by Segnitz,[1] "a thermometer might be implicated." In both cases the perforation occurred in the region of

the cul-de-sac at the level of the peritoneal reflection on the rectum. Segnitz, in his article which covers details of diagnosis and treatment of such perforations, states that this site is fairly constant regardless of the patient's age.

In this case the temperature was taken with use of approved technique, and no difficulties or unusual happenings were noted. Therefore, if this perforation was accidentally caused by a thermometer, it would seem that on occasion the normal rectum of a newborn infant may be easily perforated and that extraordinary care should be exercised when taking the temperature by rectum. It would also seem advisable that future editions of pediatric and nursing textbooks mention this possible complication of taking rectal temperatures and that consideration should be given to taking the temperature by axilla in the neonate.

Summary

A report and discussion of the second case of accidental neonatal transanal perforation of the rectum is presented.

De Witt Army Hospital.

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Abstracts from Current Literature

American Heart Journal, St. Louis
Abstracted by F. Kathryn Edwards, M.D.

56, No. 6 (Dec.) 1958

A Method for Indirect Pulse Recording, and Its Use in the Diagnosis of Aortic Stenosis. Harold L. Karpman.—p. 799.
The Electrocardiogram in Scleroderma: Analysis of Sixty Cases and Review of the Literature. Jorge Escudero and Ellen McDevitt.—p. 846.
Combined Auricular and Ventricular Septal Defects: A Study of Five Cases with Postmortem Confirmation in Three. J. Espino-Vela, B. Portillo, V. Rubio, and S. Aranda.—p. 856.
Pneumococcal Endocarditis. J. M. Ruegsegger.—p. 867.
* Valvular Pulmonic Stenosis: Auscultatory and Phonocardiographic Characteristic. Lamar Crevasse and R. Bruce Logue.—p. 898.
Congenital Stenosis of Pulmonary Veins at Their Atrial Junctions. Frank E. Sherman, William F. Stengel, and S. Richard Bauersfeld.—p. 908.

Valvular Pulmonic Stenosis: Auscultatory and Phonocardiographic Characteristics.—From the auscultatory and phonocardiographic point of view, valvular pulmonic stenosis may be divided into three groups: mild stenosis, moderate stenosis, and severe stenosis.

Mild Stenosis.—A pulmonic systolic ejection murmur heard soon after birth is present. This murmur may become louder with increasing age. The loudness of the murmur is not an indication of the severity of the stenosis. A thrill may be present over the pulmonic area. The first heart sound is almost always followed by an early systolic ejection sound which gives the impression of wide splitting of the first heart sound. The systolic ejection sound varies with respiration, becoming louder with deep expiration. This sound is followed by a systolic ejection murmur.

The pulmonic second sound is split more widely than normal, the pulmonary closure sound being 0.03 to 0.06 seconds later than aortic closure sound. This widening may be increased with inspiration. The x-rays of the heart are normal except for poststenotic dilatation of the pulmonary artery. The electrocardiogram is normal, or has minimal signs of right ventricular hypertrophy.

Moderate Stenosis.—In moderate pulmonic stenosis the ejection sound is usually present. The pulmonic closure sound is delayed further, being 0.06 to 0.10 seconds later than aortic closure. The systolic murmur is maximum in mid to late systole. The x-ray usually shows right ventricular hypertrophy.

Severe Stenosis.—The systolic murmur is delayed and is maximum in late systole, frequently extending past the aortic closure sound. With severe stenosis and heart failure the murmur may be absent. The x-ray shows right ventricular hypertrophy and decreased pulmonary blood flow. The pulmonic closure sound is more delayed, usually being 0.10 to 0.14 seconds later than aortic closure. The pulmonic ejection sound is frequently absent.

In mild pulmonic stenosis the pressure in the right ventricle is usually below 60 mm. Hg. In moderate pulmonic stenosis the right ventricle pressure is 60-100 mm. Hg. Severe pulmonic stenosis is associated with right ventricular pressure over 100 mm. Hg.

The authors believe the pulmonic ejection sound which disappears with inspiration and reappears with expiration is related to mechanical alteration in the initial tension of the poststenotic pulmonary artery produced by respiration.

American Journal of Medicine, New York
Abstracted by Hugo Dunlap Smith, M.D.

24, No. 5 (May) 1958

Electron Microscopy of the Kidney. Johannes Rhodin.—p. 661.
* Kidney Biopsies. Claus Brun and Flemming Raaschou.—p. 676.
Some Reflections on Mechanisms of Action of Diuretics. Robert F. Pitts.—p. 745.
The Kidney in Potassium Depletion. Arnold S. Relman and William B. Schwartz.—p. 764.
Pathogenesis and Management of Hepatic Coma. Sheila Sherlock.—p. 805.

Kidney Biopsies.—As part of a symposium on renal physiology, Brun and Raaschou review the status of percutaneous renal biopsy as a clinical and research tool. Little precise data are given concerning the results of the procedure; rather this report summarizes the ways in which 1,800 reported renal biopsies have been helpful. Various authors have obtained between 58% and 100% successful biopsy material, generally 75%-80%. The only universally accepted contraindications to the procedure are (1) a hemorrhagic diathesis; (2) the presence of only one kidney, and (3) the presence of an agitated or uncooperative patient if general anesthesia is not to be used. Hemodialysis should not be performed sooner than 48-72 hours after biopsy. Complications have been few. The authors observed gross hematuria on the day of biopsy in 7.9% of 510 biopsies, ureteral colic due to clots in 1%, and in two patients each, shock which reversed after blood transfusion and major but transient decline in kidney function following the biopsy. No deaths occurred in their series. Comment is made concerning three reports of death following renal biopsy.

In acute renal shutdown, renal biopsy has been of aid in connection with the use of hemodialysis; if only tubular lesions are demonstrated, the shutdown is more likely to be reversible. Frank tubular necrosis is infrequent even in severe anuria. In adults with the nephrotic syndrome, renal biopsy is of great value in distinguishing the various underlying diseases causing the disorder and in selecting those patients most likely to respond to ACTH and cortisone. The renal lesions of systemic lupus erythematosus which may be distinguished by renal biopsy from those of chronic glomerulonephritis have been shown not to be modified during corticosteroid therapy. Although in one series positive bacterial culture of biopsy material from patients with chronic pyelonephritis was obtained infrequently, good correlation between morphology and function was observed. Another group of investigators cultivated bacteria from the biopsy specimens from patients with hematuria and proteinuria but no clinical indications of pyelonephritis; antibiotic therapy then provided an apparent cure.

24, No. 6 (June) 1958

* New Concepts in the Evaluation of Intersex and Infertility. Donald K. Briggs and Herbert S. Kupperman.—p. 915.

* Physical Therapeutic Measures in the Treatment of Chronic Bronchopulmonary Disorders: Methods for Breathing Training. William F. Miller.—p. 929.

The Surgery of Portal Cirrhosis of the Liver. Robert R. Linton.—p. 941.

Acquired Fibrinogenopenia. Herbert S. Bowman.—p. 967.

New Concepts in the Evaluation of Intersex and Infertility.—The chromosomal sex of an individual may be ascertained from the appearance of the chromatin in cells of various body tissues, the presence of particular chromatin condensations ("drumsticks") indicating a genetic female. Although the sex pattern has been universally consistent in all tissues studied in an individual patient, the nuclei of neutrophic leukocytes are of value because of their easy availability. The application of this technique to problems of intersex and infertility has been of assistance in prognosis and management. In the syndrome of gonadal dysgenesis, the finding of a male chromatin pattern in a feminine-appearing patient aids in the diagnosis and indicates certain infertility, but should not be an indication to attempt to rear the patient as a male. Similarly some apparent males with gonadal aplasia or with Klinefelter's syndrome may be shown to be genetic females; again the findings indicate that infertility is inevitable, but in these cases the patients should be raised as males with supportive androgen therapy and plastic surgery as needed. The finding of a female chromosomal pattern in a newborn with a large phallus, hypospadias, and empty scrotum may lead to an earlier diagnosis of the adrenogenital syndrome and can assist in determining the sex of rearing. Such patients when given adequate corticosteroid therapy and plastic surgery may become fertile. On the other hand, the chromatin sex pattern should not be allowed to guide too completely the future clinical management of a patient; clinical judgment concerning the potential functioning of the phallus must also be considered. Also reversal of the sex of rearing is unwise if accomplished after early infancy.

Physical Therapeutic Measures in the Treatment of Chronic Bronchopulmonary Disorders: Methods for Breathing Training.—Expiratory difficulty in such chronic pulmonary diseases as asthma and bronchiectasis results from air trapping in the lungs. Exertion, apprehension, dyspnea, and cough lead to increasing air trapping, further overdistention of alveolar spaces, and exaggeration of dyspnea by decreasing the efficiency of respiratory effort. Coughing particularly precipitates increased air trapping since obstruction to the egress of air during coughing results from premature collapse of air passages owing to decreased elastic forces supporting the airways. Whereas drugs alone cannot reverse these mechanical

events, progressive failure of activity tolerance and of gas exchange and an increase in the work of breathing have been slowed or reversed by means of physiotherapy and breathing training in combination with pharmacologic measures. Such training requires a prolonged and extensive education program. The initial steps are to teach the patient concerning his illness and the pathologic physiology of his respiration. In addition, training in muscle relaxation and in quiet, abdominal breathing is begun. The breathing exercise is started with expiration using an arm across the chest to increase the expiratory effort, and, as is emphasized again when coughing is taught, with the lips held pursed during expiration so that a slight increase in intraluminal pressure will occur to prevent the premature collapse of the airways. Stress is placed upon not using the chest muscles during inspiration. The patient lies flat or even in the head-down position in order to increase the effectiveness of the diaphragmatic movement. Subsequently increased expiratory efforts are accomplished by compression of the abdomen, first manually and later through the use of abdominal supports. The patient next is taught to accomplish his new form of breathing in the upright position and then to perform walking and other activities in rhythm with the abdominal breathing. Finally corrective postural exercises and physical therapy to strengthen the accessory muscles of respiration are provided.

Comment: Although this paper describes the use of breathing exercises in adults with emphysema, many of the benefits could be obtained equally in older children. In the case of 3- to 7-year-olds, both the child and his parents would have to participate in the training program. Difficult as the program may sound, it could be of major value to children with fibrocystic disease or with asthma, particularly if begun before emphysema is too marked.

25, No. 1 (July) 1958

The Pathogenesis of Pulmonary Emphysema. K. H. McLean.—p. 62.
"Treatment of Tuberculosis Today: A Five Year Report. Albert R. Allen.—p. 75.
Adult Agammaglobulinemia Associated with Multiple Congenital Anomalies. Samuel Zelman and Hans Lewin.—p. 150.

Treatment of Tuberculosis Today: A Five Year Report.—Triple drug therapy using INH, PAS, and streptomycin was given to 330 consecutive cases of bacteriologically proved and previously untreated tuberculosis. Of the patients 17% were under 18 years of age and 11% had extrapulmonary tuberculosis. Only modified bed rest was enforced, and cafeteria privileges were allowed as soon as patients were physically able to ambulate. After discharge all patients returned to their previous activities or jobs regardless of the physical activity involved. Surgical resection was performed in 142 patients, most commonly, for one of the following indications: (1) positive cultures after three months of combined drug therapy, (2) conditions in which reactivation had been found to be common, i. e., endobronchial tuberculosis, bronchiectasis, caseous masses 2 cm. or larger in size, and cavitary disease, and (3) reactivated disease. Follow-up examination included gastric cultures which gave the first sign of reactivation in 14 patients preceding x-ray changes or positive sputum smears and cultures by as much as a year.

With this regimen 84% of the patients had negative cultures after four months. Reactivation was found in 8.5%, occurring only in the moderately and far advanced cases and being less frequent among those treated surgically. Three per cent of the 330 died of tuberculosis, 5 of the 6 medical deaths being in children with tuberculous meningitis. Whereas 3% of the patients had organisms resistant to one or more of the drugs at the time of admission, the incidence of new patients with resistant organisms did not increase with the passage of time. However, if a patient's cultures continued to be positive, INH-resistant organisms appeared after the first 6 months and streptomycin-resistant organisms between 9 and 18 months after the start of drug therapy. Cultures and smears of the resected lesions yielded positive results in 26% of the patients who had had negative gastric cultures prior to surgery. This fact supports the conclusion that reactivation is due to the presence of virulent, viable tubercle baccilli in infected tissue into which the drugs cannot penetrate.

This therapeutic program has resulted in a 70% reduction in the average length of hospital stay, a 50% reduction in the total cost of hospitalization, and a great saving to welfare departments due to the prompt return of patients to their gainful occupations. When compared to a large series of patients treated elsewhere as outpatients, the results showed a striking improvement.

25, No. 2 (Aug.) 1958

Agranulocytosis Following Administration of Phenothiazine Derivatives. Anthony V. Pisciotta, Shirley Ebbe, Edward J. Lennon, Gloria Olsen Metzger and Frederick W. Madison.—p. 210.
Pathological Effects of Cerebral Anoxia. Leo Krainer.—p. 258.

American Journal of Orthopsychiatry, New York
Abstracted by Kurt Glaser, M.D.

28, No. 2 (April) 1958

Basic Principles of Child Rearing in the Soviet Union: Firsthand Impressions of an American Observer. Herschel Alt.—p. 223.
The Significance of Atypical Postural and Grasping Behavior During the First Year of Life. Liselotte K. Fischer.—p. 368.
Psychiatric Study of Mentally Retarded Children of Preschool Age: Report on First and Second Years of a Three-Year Project. Katherine F. Woodward, Miriam G. Siegel and Marjorie J. Eustis.—p. 376.
* Hysteria in Childhood. James T. Proctor. Discussant: Henry I. Schneer.—p. 394.
Psychiatric Observations of Children with Cleft Palate. Veronica B. Tisza, Betty Selverstone, Gershen Rosenblum, and Nancy Hanlon.—p. 416.

Hysteria in Childhood.—Of 191 unselected cases of the child psychiatric unit of the University of North Carolina School of Medicine, 25 cases (13%) of conversion and/or dissociative reactions were discovered. Sixty-eight references from the literature are reviewed, and in comparison with these the author observed the high incidence and dramatic nature of the cases seen in North Carolina.

Of the 25 cases only 1 is still in treatment and only 2 have been discontinued by agreement. The majority had withdrawn from clinic contact after improvement or disappearance of the symptom. At times the symptom could be alleviated easily by strong positive suggestion; hypnosis, amytal, followed by abreaction, support and reassurance have been used successfully. However, follow-up studies reveal the high incidence of subsequent "unnecessary hospitalizations, operations and other illness" so that the author feels that psychotherapy aimed at altering the underlying pathology is indicated.

A possible examination for the high incidence in the area described might be the cultural characteristics of a primitive, highly superstitious, magically thinking population with very repressive attitudes toward smoking, drinking, and sex, and at the same time early stimulation of the child through frequent discussion of the original sin, exposure to the primal scene, and sleeping in the same bed with parents of the opposite sex to advanced age. The cause for the occurrence of a hysterical neurosis may well be a composite of constitutional factors, early ego development and mother-child relationship disturbances and "environmental factors and repressions occurring at the oedipal level."

28, No. 3 (July) 1958

* Psychiatric Teaching Programs in Pediatric Settings. Workshop, 1957. Henry H. Work, Chairman; Paul E. Baer, Ingeborg B. Snyder, George E. Gardner, John R. Blitzer, and Jo Ann Wilson.—p. 506.
The Psychodynamics of Male Adolescent Delinquency. Eugene I. Falstein.—p. 613.

Psychiatric Teaching Programs in Pediatric Settings: Workshop, 1957: An Analysis of the Educative Process in Interdisciplinary Teaching of Mental Health Concepts in a Pediatric Setting.—The learning process of mental health problems for the pediatric resident depends on the intellect, attitudes, and personality of the resident, the methods of teaching and "factors that affect the mental processes in learning and teaching." The authors report on their experience in the Department of Pediatrics, State University of Iowa College of Medicine, over a period of three years and on information from other projects.

Inhibiting and facilitating factors occurred in areas of "subject matter, individual differences between students, bias, role conflicts, the instructors and the administration of the project."

Because of the intimacy and personal nature of the subject matter it lends itself to the development of anxiety in the resident. The degree of anxiety which may be generated by a certain type of material depends on the student's earlier experiences and personality structure. His reaction to such anxiety-producing material may make him more dependent, hostile or withdrawn, both with the patient and the instructor.

The resident's bias, such as his attitude toward authority, the degree of superstition and prejudice about mental processes and psychiatry, will influence his receptiveness toward the learning process. His own attitude again will be strongly influenced by the attitude of senior

faculty members toward psychiatry. The resident's position in the hospital as a full-fledged physician, a teacher of students and a student himself is confusing and must be taken into account in the application of teaching methods. Thus the presence of students at a staff conference may interfere with the resident's willingness to ask questions or his receptiveness to criticism. The difference in approach toward medical problems using authority and dependence versus the approach in child guidance using understanding and joint problem solving needs clarification in the teaching approach. The personality of the instructor, the clarification of his role in the child guidance team, in the pediatric setting and on the faculty will influence his effectiveness as a teacher, and so will the degree of support he receives from administration and senior staff members.

Teaching methods were modified as the experience of the group increased, and were influenced by the number, personality, and training of the team members. Weekly staff conferences of the child guidance unit were found to have decreasing attraction after the novelty wore off. Fewer, better prepared meetings found less resistance. Group meetings for residents only were found unsatisfactory. Individual supervision of the residents, their inclusion in the staff conferences on their own cases, work of the resident with a child or parent in the clinic were found satisfactory but needed adaptation to the resistance, interests, and degree of sophistication of the resident. The willingness of the child guidance personnel to give service to patients strongly influenced the resident's attitude toward the team as well as toward his motivation to learn.

THE ESTABLISHMENT OF CHILD PSYCHIATRY PROGRAMS IN A CHILDREN'S HOSPITAL. George E. Gardner. This article describes administrative problems connected with the establishment of a department of child psychiatry in a children's hospital.

THE PSYCHIATRISTS'S JOB IN A CHILDREN'S HOSPITAL: HIS ROLE AS AN EDUCATOR. John R. Blitzer. A program of "teaching-consultations" by a child psychiatrist in the pediatric clinic is described. In the experience of the author the pediatric resident followed 80% of all cases discussed, 10% were referred to the psychiatric clinic and 10% to other agencies. By this process the pediatric resident learns criteria by which to decide which patients to treat himself and which to refer, and also techniques useful in his own pediatric practice. Well baby clinics and a new family health program have also been used for teaching purposes, mainly in the areas of interpersonal relationships.

JOINT PEDIATRIC AND PSYCHIATRIC CARE OF THE HOSPITALIZED CHILD. Jo Ann Wilson. The consultant psychiatrist has two functions in a pediatric ward: 1) to advise in problems connected with the fact of hospitalization—not with a specific disease—and 2) to treat children with "so-called psychosomatic problems." In the first category the pediatrician remains the child's doctor and the psychiatrist advises the physician, while in the second category the psychiatrist becomes the child's doctor. Cases are reported to illustrate these two functions.

American Journal of Pathology, Ann Arbor, Mich.

Abstracted by Jay Bernstein, M.D.

34, No. 6 (Nov.-Dec.) 1958

Pulmonary Capillary Proliferation Induced by Oxygen Inhalation. Philip C. Pratt.—p. 1033.

The Effects of Staphylococcal Toxin on the Lungs of Rabbits. J. R. Jackson, R. J. Gibbons, and Desmond Magner.—p. 1051.

* Enhanced Susceptibility of Proliferating Endothelium to Salivary Gland Virus Under Naturally Occurring and Experimental Conditions. F. Stephen Vogel.—p. 1069.

Isothiocyanate Compounds as Fluorescent Labeling Agents for Immune Serum. J. L. Riggs, R. J. Seiwald, J. H. Burckhalter, C. M. Downs, and T. G. Metcalf.—p. 1081.

Iron Storage: I. The Influence of Time on the Redistribution of Excess Storage Iron. Arne Shoden and Phillip Sturgeon.—p. 1139.

Lipoblastomatosis: A Tumor of Fetal Fat Different from Hibernoma. Frank Vellios, José Baez, and Harris B. Shumacker.—p. 1149.

Enhanced Susceptibility of Proliferating Endothelium to Salivary Gland Virus Under Naturally Occurring and Experimental Conditions.—In the case of a 10-year-old boy with a febrile course of 10 weeks' duration, examination of a liver biopsy and of tissues obtained at postmortem examination disclosed the presence of histologically typical cytomegalic inclusion disease. Affected cells were seen in the heart, lungs, gastrointestinal tract, pancreas, liver, kidneys, adrenals, salivary glands, skeletal muscle, and central nervous system. The characteristic large cells with intranuclear inclusions were associated with infiltrates of inflammatory

cells. A conspicuous feature was the presence of inclusions in proliferating endothelial and mesothelial cells in areas of chronic peritonitis and absence of these in endothelium elsewhere. Subsequent investigation with the mouse strain of salivary gland virus indicated that the proliferating cells associated with areas of chronic inflammation in experimental animals were susceptible to virus infestation as judged by the production of intranuclear inclusions. In the experimental animals as well as in the autopsied case, intranuclear inclusions were not produced in nonproliferating endothelium.

American Review of Tuberculosis and Pulmonary Diseases, New York

Abstracted by Edwin L. Kendig Jr., M.D.

78, No. 6 (Dec.) 1958

* The Stability of the Tuberculin Reaction. Solomon Kunofsky and Julius Katz.—p. 862.
A Five-Year Pilot Study of Tuberculin Testing in Honolulu Schools: Progress Report of the First Two Years of Observation. Robert H. Marks, George Tokuyama, and Agnes Peterson.—p. 871.
Chemical Analysis of the Role of Humoral Factors in Native and Acquired Resistance to Tuberculosis. Shunsaku Oshima, Yutaka Fujita, Atsuko Takeoka, Michiro Nakajima, and Shusuke Tsuji.—p. 884.
Preliminary Observations on the Development of Atypical (Chromogenic) Variants of the H37Rv Strain of M. Tuberculosis Under the Influence of Streptomycin and Isoniazid in Vitro. M. S. Tarshis.—p. 921.
The Cultivation of the Bacille-Calmette-Guérin Strain of M. Tuberculosis (BCG). T. F. Lenert et al.—p. 934.
The Biologic Activity of Crude Extracts of BCG. G. L. Hobby et al.—p. 939.
Comparison of Isoniazid Concentrations in the Blood of People of Japanese and European Descent. Therapeutic and Genetic Implications. H. W. Harris et al.—p. 944.

The Stability of the Tuberculin Reaction.—Although there are many reports in the literature of the frequency of tuberculin conversion, there is little regarding the frequency with which tuberculin hypersensitivity is decreased or lost. In a study of patients in two schools for mental defectives of the New York State Department of Mental Hygiene, the Newark State School, and Letchworth Village, the authors found that the tuberculin reaction was quite unstable and often disappeared. It is their feeling that one of the major causes of this instability is probably the variation in exposure to infectious tuberculosis, with corresponding variations in the restimulating effect upon tuberculin sensitivity.

Annals of Internal Medicine, Lancaster, Pa.

Abstracted by Brian Kiely, M.D.

47, No. 1 (July) 1957

Observations on the Nature of the Auto-Antibodies in a Case of Acquired Hemolytic Anemia. Alexander S. Wiener, Eve B. Gordon, and Erich Russow.—p. 1.
Micrococcal Bacteremia Without Endocarditis: Clinical Data and Therapeutic Considerations in 109 Cases. Alexander Schirger, William J. Martin, and Donald R. Nichols.—p. 39.
Heart Disease of Unknown Cause in Siblings. James H. Averill, Raymond V. Randall, Ellis Joffe, and Paul D. White.—p. 49.
The Prevalence of Antibiotically Treated People. Janet R. Kinney.—p. 71.
Acute Intermittent Porphyria in Identical Twins. Emmett L. Kehoe, Herman Rudensky, and William W. Reynolds.—p. 131.
Editorial: The Newer Respiratory Viruses.—p. 178.

Blood, New York

Abstracted by Audrey K. Brown, M.D.

13, No. 4 (April) 1958

* Studies on Glutathione Stability in Erythrocytes of Cases with Past History of Favism or Sulfa-Drug-Induced Hemolysis. A. Szeinberg, Y. Asher, and Chaim Sheba.—p. 348.
The Nature and Significance of Megaloblastic Blood Formation. Edward H. Reisner Jr.—p. 313.
Sickle Cell-Thalassemia Disease in Jamaica. J. E. MacIver, L. N. Went, and E. K. Cruickshank.—p. 359.

Studies on Glutathione Stability in Erythrocytes of Cases with Past History of Favism or Sulfa-Drug-Induced Hemolysis.—Erythrocytes of patients with a past history of favism or hemolytic anemia were found previously by the authors to have low levels of reduced glutathione. This was an inherited abnormality. The present study deals with application of Beutler's glutathione stability test (comparison of the level of reduced glutathione in red cells before and after two hours' incubation with acetylphenylhydrazine) to the erythrocytes of these patients, as well as reporting the effect of added glucose to the stability of glutathione.

The authors found that in all test cases, as well as in a large proportion of their relatives, the erythrocyte glutathione level was unstable when incubated with acetylphenylhydrazine. This finding suggests that the defect in erythrocytes of persons sensitive to primaquine described by Beutler and persons sensitive to sulfonamides or Vicia faba in Israel is similar. Preliminary studies indicate that there is also a deficiency of glucose-6-phosphate dehydrogenase in erythrocytes of this latter group as described by Carson et al. and Beutler et al. in primaquine-sensitive individuals.

Further the authors found that the glutathione stability test of Beutler served to distinguish the erythrocytes of test cases, provided the interpretation was based on the final concentration of glutathione after the incubation with acetylphenylhydrazine. The decrease of reduced glutathione level in abnormal cells incubated with acetylphenylhydrazine could not be prevented by the addition of glucose. The red cell defects described seem to be confined in the Jewish population to persons of Seshardic origin.

Boletín Médico del Hospital Infantil, México, D. F.

Abstracted by Mary Allen, M.D.

15, No. 3 (June) 1958

Editorial: Scientific Investigation in the Hospital Infantil de México. Jesus Kumate.—p. 347.

Wilms Tumor: Review of 37 Cases. Carlos Sarinana, Jesus Castenada, Jorge Alamillo, and Jose Luis Degado.—p. 351.

Mortality from Diarrhea in the Infants Service of Hospital Infantil de Mexico. Nelime Basile and J. A. de la Torre.—p. 361.

* Physiopathology of Salmonellosis: VII. Levels of Properdin in Typhoid. Julio Carnillo, Jesus Kumate, Gustavo Vivar, and Luis Rangel Rivera, with technical assistance of Virginia Vasquez.—p. 369.

Respiratory Problems in the Premature Infant: II. Oximetric and Hematological Values in "Healthy" Premature Infants During the First Week of Life. J. Alvarez de los Cobos, E. Jurado García and Josephina Sagaón Ramirez, technical assistance of Enrique León Villalba.—p. 377. (There is an English translation of this article.)

Clinical Pathological Conferences: Case A-57, No. 87: Lymphosarcoma in Six-Year-Old Girl: Case A-56, No. 119: Maximiliano Salas, Higimio Esparza, Octavis Angulo, and Kurt Ambrosiuss.—p. 405.

Socio-Cultural Profile of Families Receiving Services at Hospital Infantil de México. Raquel C. de Berman.—p. 423.

Fluid and Electrolyte Therapy in the Emergency Service of Hospital Infantile. Nehme Basila and Armando Frances Gomez.—p. 429.

Physiopathology of Salmonellosis: VII. Levels of Properdin in Typhoid.—In the seventh report on the physiopathology of typhoid the authors studied properdin levels in children with typhoid. The technique used was that described by Pillener in 1955.

Controls were 31 adult donors at the blood bank at the Hospital Infantil in Mexico City and 31 normal healthy children.

The serial serum properdin levels in children were found to average 3.9 units per cubic centimeter in children and 8.5 in adults. The difference is statistically significant.

In eight cases of typhoid in hospitalized children, increased values were found beginning at the third week of the disease.

The properdin showed an inverse exponential type correlation with body temperature which was statistically significant. There was also direct lineal correlation with agglutination titers as a whole.

In one case which showed clinical and bacteriological resistance to antibiotics, low agglutination titers also showed negative properdin values.

The findings as a whole are interpreted as the result of the endotoxin of S. typhosa which caused an immediate drop in properdin levels followed by a rise later on.

The probable role of other intracellular components, which have been shown to increase in the blood during the acute stage of typhoid, is discussed.

15, No. 4 (July-Aug.) 1958

Editorial: Pediatrics and General Medicine. Frederico Gómez.—p. 471.

Studies on the Use of Deodorized Fish Flour in Nutrition. Frederico Gómez, Rafael Ramos-Galván, Joaquin Cravioto, Silvestre Fienk and Isabela Labardine.—p. 475. (This article is translated into English.)

The Feeding of the Malnourished Child. Rafael Ramos-Galván and Joaquin Croviots.—p. 495.

The Teaching of Pediatrics in the Hospital Infantil de México. Alejandro Aquirre.—p. 503.

* Clinical Cases: 1. Tridermal Teratoma of the Stomach. Carlos Sarinana, Arturo Silva Cuevas, and Higinio Esparza—p. 529.

2. Studies of Elevated Eosinophilia with Visceral Manifestation of Obscure Origin: Bronchopneumonia Due to Ascaris. Lumbricoides. Francisco Brozi, Raphael Soti, Samuel Daontes, Jaime Portilla, Judith Vasquez, and Olga Castrejon.—p. 537.

Clinical Pathological Conferences: Hyaline Membrane with Gastric Perforation. Astrocytoma in a Six-Year-Old Boy. Maximiliano Salas, Hygenio Esparza, Octavio Angulo, and Kurt Ambrosius.—p. 547.
Metabolism of Biliary Pigments. Jesus Kumata.—p. 561.

Clinical Cases: 1. Tridermal Teratoma of the Stomach.—The case of an infant 45 days old who had a tridermal teratoma of the stomach is reported.

The infant was noted to have a progressively increasing tumor mass in the abdomen when 20 days old. Later there was difficult breathing, and a few days later he became pale and black stools were passed.

The physical examination showed an infant weighing 5,365 gm., who had hyperpnea, distended abdomen with a network of distended superficial veins. In the upper quadrant there was a lobulated mass which had indurated areas and extended from the diaphragm to the crest of the ilium.

The differential diagnosis between Wilms tumor, neuroblastoma, and anomaly of the gastrointestinal system could be made only by laparotomy.

During the operation, a blood transfusion was given, and a multilocular teratoma containing tissues derived from mesoderm, entoderm, and ectoderm embryonal layers was removed.

It was covered with peritoneum and was attached to the lower posterior portion of the stomach. It was well encapsulated but a partial gastrectomy was performed because it had invaded the posterior wall of the stomach.

The tumor weighed 990 gm. and was 17 cm. in diameter. This was almost a fifth of the child's total weight.

Photographs showing gross appearance of the tumor, pathological sections, and the baby two months postoperatively are included.

The child recovered without sequelae.

Bulletin of the Johns Hopkins Hospital, Baltimore
Abstracted by Thomas K. Oliver Jr., M.D.

103, No. 4 (Oct.) 1958

Hyper-Immunization of Man. Richard H. Peeler, Leighton E. Cluff, and Robert W. Trever.—p. 183.

Canadian Medical Association Journal, Montreal
Abstracted by H. M. Keith, M.D.

79, No. 10 (Nov. 15) 1958

* The Prevention of Acetylsalicylic Acid Poisonings. Henri J. Breault.—p. 825.
Accidental Poisoning in Childhood.—p. 846.
Psychological Aspects of Atopic Dermatitis in Children. E. D. Wittkower and B. R. Hunt.—p. 810.

The Prevention of Acetylsalicylic Acid Poisonings.—In Windsor, Ont., one-half of all drug poisonings in children were due to acetylsalicylic acid. During the same period similar poisonings occurred throughout Canada and the United States in much the same ratio. It is "particularly the candy flavoured type for children, that is the worst trouble maker." The author quotes the "Precautions against Salicylates" published in *The Journal of the American Medical Association* in July, 1955, including recommendations in regard to packaging, and feels that the pharmaceutical firms should adopt without fail these regulations.

79, No. 11 (Dec. 1) 1958

* The Effect of Nystatin (Mycostatin) on Neonatal Candidiasis (Thrush): A Method of Eradicating Thrush from Hospital Nurseries. L. J. Harris, H. G. Pritzker, A. Eisen, J. W. Steiner, and L. Shack.—p. 891.
* School Phobias. F. A. Dunsworth.—p. 932.
A Study of Enuresis. J. B. J. McKendry, L. LaForest, H. A. Williams, and Eleanor Davidson.—p. 899.

The Effect of Nystatin (Mycostatin) on Neonatal Candidiasis (Thrush): A Method of Eradicating Thrush From Hospital Nurseries.—The authors find that thrush can be completely eliminated from hospital nurseries by the daily instillation of 1.0 cc. (100,000 units) of nystatin into the mouth of each infant. In a final note they state that this treatment given twice, once on the second and once on the fifth day of life, was equally effective. They demonstrated a high degree of correlation between positive vaginal cultures in the mothers, and positive oral cultures and clinical thrush in the infants. The administration of the nystatin was simple, and no toxic or other side-effects were noted. Squibb Mycostatin was used.

School Phobias.—School phobias occur fairly frequently, perhaps more frequently than would appear on casual observation. Such a phobia is specific in type and is a thinly disguised displacement of anxiety in most cases. The anxiety is mainly a separation anxiety, and involves either (*a*) maternal rejection, (*b*) preference of a parent for another sibling or (*c*) an extreme overdependency on an overprotecting mother. Symptoms may consist of direct expression of fear, or somatic symptoms, such as nausea, vomiting, or headaches.

Treatment appears to be (*a*) firm decision that the child is to return to school and (*b*) the area of psychologic disturbance must be dealt with. These are discussed in some detail, and the author emphasizes that prevention is more important than treatment and that an adequate assessment of the total situation must be made.

Journal of Clinical Endocrinology and Metabolism, Springfield, Ill.

Abstracted by Judson J. Van Wyk, M.D.

18, No. 6 (June) 1958

* Masculinization of the Female Fetus Associated with Administration of Progestins During Gestation: Non-Adrenal Female Pseudohermaphrodism. L. Wilkins, H. W. Jones Jr., G. H. Holman, and R. S. Stempfel Jr.—p. 559.

Stimulation and Suppression of the Adrenal Cortex in Cushing's Syndrome. J. D. Nabarro, A. Moxham, and G. Walker.—p. 586.

Extraction and Purification of Human Pituitary Gonadotropin. A. Albert, S. Kelly, L. Silver, and J. Kobi.—p. 600.

Effect of Exogenous Adrenocortical Hormones and States of Adrenal Dysfunction on Body Sodium and Potassium Composition. W. L. Avons, B. Nusimovich, R. J. Vanderlinde, and G. W. Thorn.—p. 611.

Relationships Between Clinical Severity of Hyperthyroidism and Results of the Thyroid Function Tests. A. L. Schultz and L. Zieve.—p. 629.

Effect of Endocrine Ablative Surgery on Urinary Excretion of 17-Ketosteroids in Advanced Cancer of the Breast. R. Hobkirk.—p. 636.

Chromatographic Procedure for Determination of Urinary Corticosteroids and C_{19} Steroids. H. Wilson, J. J. Borris, and M. M. Garrison.—p. 643.

Metabolism of Cortisol-C^{14} in Subjects with Addison's Disease. A. A. Sanberg and W. R. Slaunwhite Jr.—p. 662.

Masculinization of the Female Fetus Associated with Administration of Progestins During Gestation: Non-Adrenal Female Pseudohermaphrodism.—Female pseudohermaphroditism not due to congenital adrenal hyperplasia is relatively rare, and most of the cases previously recorded have been associated with other congenital anomalies. The present paper reports 21 additional cases in which there were no associated congenital anomalies and in which the only anomaly was an enlarged clitoris with a varying degree of fusion of the labioscrotal folds. In some instances the baby was initially considered to be a male with hypospadias. The vagina, cervix, uterus, tubes, and ovaries were normal in these patients, although in some instances the vagina opened into a urogenital sinus, or had no visible exterior outlet. All of the patients in this series had a female chromatin pattern, and there was no postnatal virilizing tendency. The 17-ketosteroid excretion was normal for the age of each of these patients.

In 15 of the cases the mother, because of threatened or habitual abortion, had been treated with ethisterone, an oral progestational agent marketed under such trade names as Pranone, Progestoral, or Lutocylol. In one case both intramuscular progesterone and oral methyltestosterone had been administered. Estrogen administered along with the other steroids did not appear to protect the fetus from masculinization. In three patients no steroids were administered during pregnancy, but in two of these the mother spontaneously developed acne, deepening of the voice, and mild hirsutism during her pregnancy.

It is emphasized that the pediatrican and obstetrican should be alert to the diagnosis of female pseudohermaphroditism in any child in whom gonads cannot be palpated in the scrotum or inguinal regions and in whom the phallus is enlarged. A female buccal smear strongly suggests this diagnosis, although a female buccal smear is occasionally encountered in true hermaphroditism. Steroid therapy during pregnancy should suggest the possibility of female pseudohermaphroditism without adrenal hyperplasia. A measurement of the 24-hour excretion of 17-ketosteroids and pregnantriol should be carried out to exclude the possibility of the adrenogenital syndrome.

The importance of this diagnosis lies in the fact that female pseudohermaphrodites with or without adrenal hyperplasia are the only hermaphroditic persons who are capable of pregnancy and child bearing. They should therefore all be reared as females.

ABSTRACTER'S NOTE: Since this paper was published, numerous similar cases have been recognized in all parts of the country. Some of the newer synthetic progestational steroids, such as 19-Nor, 17-ethynyltestosterone, have been associated with cases of female pseudohermaphroditism not due to adrenal hyperplasia.

18, No. 7 (July) 1958

* Pituitary Dwarfism: Diagnosis and Treatment. M. M. Martin and L. Wilkins.—p. 679.
* Absence of 21-Dehydroxylation in Congenital Adrenal Hyperplasia. D. K. Fukushima and T. F. Gallagher.—p. 694.
Abnormal TSH in Serum in Some Cases of Thyrotoxicosis. D. D. Adams.—p. 699.
Metabolism of 3:3':5'-Triiodothyronine in Man. J. T. Dunn and J. B. Stanbury.—p. 713.
Physiologic Effects of 1-Triiodothyronine. E. H. Strisower, J. W. Gofman, B. Strisower, and O. de Lalla.—p. 721.
Assessment of Functional Capacity of Adrenal Cortex: I. Establishment of Normal Values. G. Birke, E. Diczfaluay, and L.-O. Plantin.—p. 736.
Diurnal Variation of Plasma 17-OHCS in Severe Brain Damage. K. Eik-Nes and L. D. Clark.—p. 764.
Probenecid in Hypoparathyroidism: Absence of Phosphaturic Response. A. Despopoulos.—p. 769.
Micro-Method for Butyl-Alcohol Extractable Hormonal Iodine in Serum. N. E. Kontaxis and D. E. Pickering.—p. 774.
Effect of an Aldosterone Antagonist on Na and K Excretion in Primary Aldosteronism. R. M. Salassa, V. R. Mattox, and M. H. Power.—p. 787.
Detection of Antithyroid Antibodies. B. H. Landing, C. D. West, and V. M. Esselborn.—p. 792.
Rapid Radioiodine Suppression Test Using Triiodothyronine. S. Dresner and N. G. Schneeberg.—p. 797.

Pituitary Dwarfism: Diagnosis and Treatment.—The diagnosis of the cause of stunted growth during childhood is one of the most difficult problems encountered by the pediatrician and endocrinologist. Out of 442 cases of dwarfism studied in the Endocrine Clinic of the Harriet Lane Home only 30 children had hypopituitarism and of these 11 had tumors in the pituitary region. Twenty-six of these cases were followed past the age of puberty and were analyzed with regard to etiology, sex incidence, time of onset of growth retardation, and frequency of impairment of target gland function. Out of 19 of the patients with idiopathic pituitary insufficiency, 18 were males. Of the seven patients with neoplasms, two were males. In four instances the growth retardation was apparent by the first year of age but more commonly it did not become manifest until the third or fourth year of age. The birth weight was usually normal.

Of the patients with idiopathic hypopituitarism, the protein-bound iodine was below 4.0 μg/100 ml. in only 6 of the 16 patients tested. More frequently it was in the low normal range. The serum cholesterol was elevated above 300 mg. % in all but four of the patients, but in none was the serum cholesterol as high as in untreated patients with primary hypothyroidism. Increased insulin sensitivity and hypoglycemic unresponsiveness were present in 9 of 17 patients tested. Excretion of a standard water load was studied in 13 patients and found to be abnormal in 8. Urinary 17-ketosteroid excretion was abnormally low in 12 of 13 patients, and the 17-hydroxy-corticosteroid excretion was similarly low in 7 out of 11 patients. Two of the patients matured sexually to some degree without treatment, and in one patient urinary follicle-stimulating hormone could be measured.

It is emphasized that is some instances where target gland function is unequivocally low the presumptive diagnosis of panhypopituitarism may be made before puberty. Certain psychological considerations suggest that in these patients treatment should be instituted at about 12-13 years of age. Where the diagnosis is in doubt treatment should be delayed until there is reasonable certainty that the case is not one of constitutionally delayed growth and adolescence.

Absence of 21-Dehydroxylation in Congenital Adrenal Hyperplasia.—Hydrocortisone-4-C^{14} was administered to a patient with congenital adrenal hyperplasia who excreted large amounts of C-21-deoxyhydrocortisone metabolites in his urine. It was found that only minute amounts of labeled C-21-deoxymetabolites were found in the next 48 hours. This paper offers further confirmation that the large amounts of C-21-deoxysteroids present in the urine of patients with congenital adrenal hyperplasia arise from failure of hydroxylation of C-21 precursors and not from deoxygenation of hydrocortisone or other C-21-oxygenated hormones.

Maandschrift voor kindergeneeskunde, Leiden, Netherlands
Abstracted by S. van Creveld, M.D.

26, No. 6 (June) 1958

The Effect of Cortisone in Infections. M. R. H. Stoppelman.—p. 181.
A Case of Benign Intracranial Hypertension. E. E. Brongers.—p. 198.

26, No. 7 (July) 1958

New Data on the Genesis of Microphthalmus. P. J. Waardenburg.—p. 220.
Congenital Afibrinogenemia. S. van Creveld and Liem Khe Hoo.—p. 227.
* Hemiplegia Spastica Infantilis and the Value of Diagnostic Trepanation. A. Biemond.—p. 238.

26, No. 9 (Sept.) 1958

Triangle Discussion in the Pediatric Clinic at Leyden on a Patient with Paradox Obstipation. G. M. H. Veeneklaas.—p. 281.
Severe Complications in Varicella. F. Kuipers and J. van der Mei.—p. 294.
The Effect of Epidemic Parotitis and Prednisone in Lipoid Nephrosis. M. Wijffels.—p. 299.
Varicella Bullosa. J. van der Mei.—p. 311.

26, No. 10 (Oct.) 1958

Hospitalization in Early Childhood: The Behaviour After Discharge. M. D. Renata Gaddini de Benedetti.—p. 317.
* On Chronic Paralysis of Respiration and the Significance of Glossopharyngeal Breathing. G. J. van Weerden and P. W. Rijnvis.—p. 327.
Congenital Non-Spherocytic Hemolytic Anemias. J. A. Kaars Sijpesteijn.—p. 336.

Hemiplegia Spastica Infantilis.—The author, head of the Department of Neurology of the University of Amsterdam, stresses the great importance of full use of the modern neurological diagnostic tests, including diagnostic trepanation, in the present medicosocial care of the spastic child. Three cases of hemiplegia spastica infantilis are reported in which a final diagnosis was made by trepanation.

On Chronic Paralysis of Respiration and the Significance of Glossopharyngeal Breathing.—The authors describe the technique of glossopharyngeal breathing. This way of breathing enables the patient with chronic respiratory paralysis to free himself from his respirator for several hours a day. Moreover, the technique provides the patient with the possibility to cough. Glossopharyngeal breathing not only improves the respiration quantitatively but also qualitatively as can be judged from capnography.

Comment: This is a very thorough investigation.

Nederlands tijdschrift voor geneeskunde, Amsterdam
Abstracted by S. van Creveld, M.D.

102, No. 21 (May 24) 1958

Decompensatio Cordis in the Infant. J. H. P. Jonxis.—p. 973.

102, No. 22 (May 31) 1958

* Acute Virus Infections of the Lower Airways in Childhood and the Syndrome of Stevens-Johnson. J. F. M. Hölscher.—p. 1025.

102, No. 23 (June 7) 1958

Hypogammaglobulinemia and Bronchiectasis. F. de Meulemeester.—p. 1076.
* Accident Mortality in the Netherlands. B. J. van den Berg.—p. 1081.

102, No. 24 (June 14) 1958

Stammering. F. Grewel.—p. 1129.
* Active Immunization Against Poliomyelitis with a Vaccine of Attenuated Virus: I. Theoretical Basis and Selection of Strains. J. D. Verlinde.—p. 1138.
* Active Immunization Against Poliomyelitis with a Vaccine of Attenuated Virus: II. First Communication on the Application of the Sabine Vaccine in the Netherlands. J. D. Verlinde, J. B. Wilterdink, B. Hofman, and A. Kret.—p. 1144.

Acute Virus Infections of the Lower Airways in Childhood and the Syndrome of Stevens-Johnson.—Description of 14 children with acute viral infections of the lower respiratory tract, complicated in 2 by the syndrome of Stevens-Johnson. The possibility of a common etiology of the two diseases seems improbable.

Accident Mortality in the Netherlands.—During the last years about 4,400 persons have died annually as a result of accidents; 1,000 of these were under 20 years of age. The curve of accident mortality by age shows different peaks, one at preschool age (1-4 years). The accident mortality for the latter age group amounts to 35 per 100,000. At all ages men have a higher accident mortality. In the last 25 years accident mortality at preschool age has decreased by 30%. The principal causes of accident mortality in children under 20 are traffic accidents and drowning.

Active Immunization Against Poliomyelitis: I. Theoretical Basis and Selection of Strains.—The theoretical basis for active immunization with live, attenuated polio virus is explained. As most reliable method of selecting suitable strains the use of single plaque progeny according to Sabin is recommended.

Active Immunization Against Poliomyelitis with Attenuated Virus: II. First Report on the Use of Sabin Vaccine in the Netherlands.—Forty persons, with and without preexisting homotype antibody, children as well as adults, were fed Sabin's highly attenuated strains of the three types of poliomyelitis virus. With only four exceptions, an asymptomatic alimentary infection and development of antibody were demonstrated in persons without preexisting high-activity homotype antibody. The duration of the alimentary infection (virus excretion) varied from 7 to 44 days. So far there seems to be no reason to assume that this method of vaccination might lead to the circulation of virus with a high neurotropic activity.

102, No. 25 (June 21) 1958

Areflexia Pupillotonia, Neurotic Syndromes and Epilepsy. A. Verjaal and A. J. de Vries.—p. 1186.
Investigation of Stool for Urobilinogen According to the Method of Terwen-Watson in Different Forms of Jaundice. K. H. Brandt.—p. 1189.
* Hemolytic Streptococci in Healthy Inmates of a Children's Home. H. C. Zanen and S. Wagenaar.—p. 1198.
Listeriosis in Mother and Child. O. Kranendonk.—p. 1202.
Meningitis Due to Listeria Monocytogenes in a Baby. G. W. van Driest and E. H. Kampelmacher.—p. 1206.

102, No. 26 (June 28) 1958

Methods of Administering Oxygen. A. M. van Leeuwen and C. M. Thomasse.—p. 1237.
The Lipidal Test, a Method for Testing the Digestion of Fats. J. A. de Fockert and J. B. Lenstra.—p. 1246.

102, No. 27 (July 5) 1958

* Nature of the Kveim Reaction and the Etiology of Besnier-Boeck Disease (Sarcoidosis). R. Kooy.—p. 1292.

102, No. 29 (July 19) 1958

* Diaphyseal Aclasis Combined with Fragilitas Ossium. J. Coenegracht and H. Naber.—p. 1398.

102, No. 30 (July 26) 1958

* Possibility of Human Infection by Pigs Suffering from Coxsackie Virus Pneumonia. J. D. Verlinde, J. Versteeg, and H. Beeuwkes.—p. 1445.

102, No. 31 (Aug. 2) 1958

* Simultaneous Mild Hemophilia and Thrombopathia in One Family. S. van Creveld, C. Everts-Coster, and H. A. Veder.—p. 1493.

102, No. 32 (Aug. 9) 1958

Disorder Caused by Hair Lotion Containing Stilboestrol. J. F. Thomson.—p. 1548.

102, No. 37 (Sept. 13) 1958

* Studies of Blood Circulation by Injection of Dye and Reflection Oximetry. L. B. van der Slikke, W. G. Zijlstra, K. K. Bossina, J. Nieveen, and G. A. Mook.—p. 1789.

102, No. 39 (Sept. 27) 1958

* Transmission of Salmonellosis Newport by Tortoises. G. D. Hemmes.—p. 1906.

102, No. 40 (Oct. 4) 1958

* An Epidemic of Pharyngoconjunctival Fever. J. van der Veen and G. van der Ploeg.—p. 1948.
Difficulties in the Diagnosis of Erythroblastosis Foetalis Due to ABO Incompatibility. L. A. Schellekens, J. C. Sellen, and J. N. J. Bakker.—p. 1954.

102, No. 41 (Oct. 11) 1958

* Bone Marrow Transplantation in the Treatment of Radiation Sickness. D. W. van Bekkum.—p. 1999.
* Requirements for Successful Grafting of Bone Marrow and Its Effects on the Host. O. Vos.—p. 2004.
* Total Body Irradiation and Bone Marrow Transplantation in the Treatment of Malignant Systemic Diseases. M. J. de Vries.—p. 2012.

102, No. 43 (Oct. 25) 1958

Umbilical Tetanus Treated with Chlorpromazine. F. J. van Rootselaar.—p. 2097.

102, No. 44 (Nov. 1) 1958

Treatment of Atresia of the Esophagus and Esophagotracheal Fistula. A. P. Brinkhorst.—p. 2144.

102, No. 45 (Nov. 8) 1958

* A Patient with Rickets. J. M. H. Veenecklaas.—p. 2205.
* Paraplegia Spastica Hereditaria. J. W. Bruins and C. H. Simonis.—p. 2210.

102, No. 46 (Nov. 15) 1958

Dysplasia Epiphysealis Multiplex. R. Ch. Ledeboer and P. J. de Meel.—p. 2257.

102, No. 49 (Dec. 4) 1958

* A Syndrome of Sporadic Cretinism with Other Congenital Anomalies ("Nervous Cretinism," Syndrome of McCarrison). G. Hellinga.—p. 2423.

102, No. 51 (Dec. 18) 1958

* The Variability of the Results of Differentiation of Cells in Blood Smears. Chr. L. Rümke.—p. 2505.

Hemolytic Streptococci in Healthy Inmates of a Children's Home.—Over a period of two years fornightly examinations of 40 children in a children's home showed that the presence of Group A hemolytic streptococci in the throats of the children varied from 2%-100%. In summer fewer children were infected than in winter. In two years seven epidemics caused by various Group A streptococci were seen; 10% were attended with illness. The children had annually an average of three nonclinical infections with new types of Streptococcus and suffered every three to four years from one streptococcal illness. The presence of Group A hemolytic streptococci in the throats of children apparently has little diagnostic significance.

Type 14 was found in 40% of 510 scarlet fever patients in Amsterdam at the time of the investigation. The use of penicillin against streptococci should be limited to severe clinical infections and to the prevention of recurrent rheumatic fever. Little benefit is expected if healthy carriers are kept home from school.

Nature of the Kveim Reaction and the Etiology of Besnier-Boeck Disease (Sarcoidosis).—Arguments are brought forward in support of the view that the Kveim reaction is the expression of a sarcoid mode of reaction in certain individuals and that the Kveim antigen does not contain specific substances.

Sarcoidosis is considered to be a syndrome which may be evoked in certain individuals by a variety of agents (silicates, beryllium, Zirkonium, Spirochetes, tubercle bacilli, and Mycobacterium leprae).

Diaphyseal Aclasis Combined with Fragilitas Ossium.—Description of two cases of diaphyseal aclasis and osteogenesis imperfecta in the two youngest children of an otherwise healthy family. One patient developed phantom tumors of both femora in the course of the disease. The other suffered from hypophyseal hypogonadism due to a craniopharyngioma.

Possibility of Human Infection by Pigs Suffering from a Coxsackie Virus Pneumonia.—A minor explosive epidemic of acute febrile and throat symptoms was observed among children of a village. For epidermiological reasons young pigs suffering from virus pneumonia were suspected of being the source of infection. A Group A Coxsackie 5 virus was repeatedly isolated from the lungs of two pigs, and the children's convalescent sera showed a very high neutralization index to this strain. After three passages this strain was myotropic for suckling mice. Intranasal inoculation of suckling-mouse carcass suspension produced virus pneumonia and specific antibody in healthy pigs.

Simultaneous Mild Hemophilia and Thrombopathia in One Family.—Description of a family with mild hemophilia A with abnormal heredity. When a member of this family married a woman from a family with frequent cases of thrombopathia, the result was a generation showing the characteristics of both hemorrhagic disorders.

Studies of Blood Circulation by Injection of Dye and Reflection Oximetry.—The blood circulation of a great many patients with congenital and acquired cardiovascular anomalies was studied with the blue dilution curve. This method is of great diagnostic value; it does not cause any trouble to the patient. A detailed description is given of the apparatus (cyclopeoxymeter of Brinkman) and the technique used. The curves obtained in various cardiovascular anomalies are analyzed.

Transmission of Salmonellosis Newport by Tortoises.—Two girls, nearly one year old, suffering from S. Newport, were infected by their tortoises (Testudo graeca). S. Newport was cultivated from stools of the children and the animals.

An Epidemic of Pharyngoconjunctival Fever.—Description of an epidemic of pharyngoconjunctival fever predominantly among children aged 8-14 and more frequent in boys than in girls.

Bone Marrow Transplantation in the Treatment of Radiation Sickness.

Requirements for Successful Grafting of Bone Marrow and Its Effect on the Host.

Total Body Irradiation and Bone Marrow Transplantation in the Treatment of Malignant Systemic Diseases.

This is a series of three important articles concerning experimental studies on total irradiation and bone-marrow transplantation going on in the Netherlands.

In the first article the therapeutic action of spleen and bone-marrow cells in irradiated animals is discussed. Under certain conditions transplantation of homologous and heterologous bone marrow has been achieved.

In the second article the factors which influence a succesful grafting of bone marrow in irradiated mice are described.

Intravenous injection of a suspension of viable bone-marrow cells gave the most favorable results.

Mice treated with homologous or heterologous bone marrow develop a disease which appears predominantly between the 30th and 80th day after irradiation and kills most of them. The pathogenesis of this disease is probably a graft antihost immunological reaction.

In the third article it is pointed out that the radiosensitivity of tumor cells remains among the determinative factors for a successful therapy. Experiments with a mouse lymphosarcoma have indicated that antibody production by a graft of foreign lymphoid cells may be a valuable adjunct in the destruction of radioresistant tumor cells.

The conditions to be fulfilled in a trial of total body irradiation and bone-marrow transplantation in man are discussed.

A Patient with Rickets.—In this clinical lecture a report is given of a combined study of a case of rickets in a baby of 6 months by pediatrician, sociologist, and psychiatrist.

Hereditary Spastic Paraplegia.—Description of a family in which symptoms of hereditary spastic paraplegia have occurred in four successive generations.

A Syndrome of Sporadic Cretinism with Other Congenital Anomalies.—In five cases of congenital absence of thyroid function, certain symptoms occurred which cannot very well be explained by thyroid hormone deficiency: retrognathia, nasal speech, progressive shortening of the sural muscles, and various anomalies of the feet.

The Variability of the Results of Differentiation of Cells in Blood Smears.—The variability of the results of differentiations of cells in blood smears is discussed, with the aid of a table (prepared by C. van Eeden). The 95% confidence limits can be found for a percentage which has been determined by differentiation of 100, 200, 500, or 1,000 cells.

Comment: This is an interesting article on the relative significance of the results of differentiation of the cells in blood smears.

New England Journal of Medicine, Boston

Abstracted by Demetrius G. Traggis, M.D.

259, No. 18 (Oct. 30) 1958

* Electrophoretic Analysis of Serum Proteins in Infants and Children: II. Serum Gamma-Globulin Levels in Selected Infections and "Hypersensitivity" Disease in Childhood. J. W. Oberman, K. O. Gregory, F. G. Burke, S. Ross, and E. C. Rice.—p. 855.

An Evaluation of Electrodiagnostic Testing. A. L. Watkins.—p. 868.

Electrophoretic Analysis of Serum Proteins in Infants and Children: II. Serum Gamma-Globulin Levels in Selected Infections and "Hypersensitivity" Diseases in Childhood.—This is the second in a series of studies on serum protein, the first having been concerned with normal values. This study concerns gamma globulin in various infections, allergic and "hypersensitivity" states. Filter-paper electrophoretic analysis was performed on sera of 239 children of varying ages suffering from selected bacterial, viral, and "hypersensitivity" diseases—27 with meningitis, 36 with other bacterial infections, 7 tuberculosis, 38 aseptic meningitis, 30 other viral diseases, 10 viral hepatitis, 33 bronchopneumonia, 8 nephrosis, 25 glomerulonephritis, 25 rheumatic fever, and 78 children proved to have repeated infections. Repeat serum specimens were obtained on 128 about a week later, except in nephrosis, where repeat specimens were taken in remission. All figures are expressed as gm/100 ml. for com-

parison. It was noted that total proteins tended to be a little low during the acute stage of the disease, when dehydration, etc., might make one expect higher values.

In meningitis one had a high value and six low (five under 7 months of age). These returned to normal. In one who responded poorly levels remained low. With miscellaneous bacterial infections 11 of 36 had high levels (chiefly in those who had involvement of lymphoid tissue); no correlation between severity of disease and level of gamma globulin. One with abnormally low level died of meningococcemia. Three of seven with tuberculosis had high levels and one other developed a high level later. The most chronic case had normal levels. Of 38 children with aseptic meningitis, 3, and of 30 with other viral diseases, 2, had elevated levels. Nine of ten with hepatitis had elevated levels. Of 33 with bronchopneumonia 4 had elevated levels and 2 had low levels. Of eight with nephrosis all had low levels in the acute stage and four continued to have low levels after diuresis. Of all children with rheumatic fever 50% had elevated levels but could not be correlated with severity, complications, ASO titers, etc. One-third of children with acute glomerulonephritis had elevated levels in first week and two-thirds in second week. Of 78 with repeated infections (URI), 9 had abnormally high levels (6 sick at the time), 17 had abnormally low levels (8 sick at the time), and 15 were in low normal ranges; no correlation between levels and history and physical examination. The authors' findings confirmed other reports of abnormal elevations in such diseases as tuberculosis, viral hepatitis, rheumatic fever, and acute glomerulonephritis. They failed to substantiate the findings of others that levels were elevated in the chronic and convalescent stages of bacterial and viral infections. The low levels in nephrosis were noted as previously reported. Another group with low values were infants under seven months with infections; yet they did well. Of interest was the fairly high percentage of children with repeated infections (URI) who had low levels (22 of 78). In general the levels of gamma globulin showed no relationship to the severity, clinical findings, or outcome.

259, No. 19 (Nov. 6) 1958

Bananas as a Low-Sodium Dietary Staple. W. E. C. Wacker, M. Margoshes, A. F. Bartholomay, and B. L. Vallee.—p. 901.
Bleeding Esophageal Varices with Polycystic Liver: Report of Three Cases. G. S. Campbell, H. D. Bick, E. P. Paulsen, P. H. Lober, C. J. Watson, and R. L. Varco.—p. 904.
Aldosterone. J. T. August, D. H. Nelson, and G. W. Thorn.—p. 917.

259, No. 20 (Nov. 13) 1958

Eosinophilic Granuloma of the Lung. Harold J. Livingston.—p. 959.
Failure of Ristocetin Therapy in Three Cases of Staphylococcal Sepsis with Bacteremia. Lowell A. Rantz and Ernest Jewetz.—p. 963.
Aldosterone (Concluded). J. Thomas August, Don H. Nelson, and George W. Thorn.—p. 967.
* Thrombophlebitis in Patients with Severe Poliomyelitis. Benjamin G. Ferris Jr., B. McNichol, and G. Sutin.—p. 971.
Effect of Meprobamate-Tridihexethyl Iodine on the Uptake of Radioactive Iodine and on the Serum Protein-Bound Iodine. Stanley Slater and Marvin Numeroff.—p. 974.
Current Concepts in Therapy.—p. 976.

Thrombophlebitis in Patients with Severe Poliomyelitis.—The authors report on 9 cases of thrombophlebitis occurring in 98 severely paralyzed patients (from poliomyelitis). Ages were from 10-31 years. All patients were in the tank respirator at the time (one also partly in rocking bed). Three cases, with obvious sources such as infected toenail and intravenous catheter, were not included in the nine.

Diagnosis was made on the basis of pain in the groin, fever, leukocytosis, and swelling of the involved leg. All nine cases occurred in the legs. In six of the nine, onset was within six weeks of admission. In six patients hemoglobin levels were elevated before thrombophlebitis occurred, and in three they were not known. In all but one, hemoglobin levels were normal after the episode. In eight of the nine, the left lower limb was involved.

Possible causes considered were the following: hypoventilation and dehydration which might lead to hemoconcentration; circulatory stasis due to prolonged immobilization, or pressure of left iliac artery on left common iliac vein, or venous obstruction due to a full rectum and sigmoid.

They recommend as early weaning as possible from the tank respirator. The authors also received answers from other centers as to the incidence of thrombophlebitis, which were as follows: 6 cases out of 1,500 from one center (severity not stated), and 5.0% and 9.4% from two other centers which handle only severely involved patients.

259, No. 22 (Nov. 27) 1958

Complication Rate in General Surgical Case: The Value of Penicillin and Streptomycin as Postoperative Prophylaxis—A Study of 511 Cases. R. Sanchez-Ubeda, E. Fernand, and L. M. Rousselot.—p. 1045.

* Etiology of the Severe Form of Idiopathic Hypercalcemia of Infancy: A Defect in Vitamin D Metabolism. F. X. Fellers and R. Schwartz.—p. 1050.

Intussusception in Infancy and Childhood: An Analysis of Seventy-Seven Cases Treated by Barium Enema. M. M. Ravitch.—p. 1058.

Abdominal Aortography. O. W. Kincaid and G. D. Davis.—p. 1967.

Etiology of the Severe Form of Idiopathic Hypercalcemia of Infancy: A Defect in Vitamin D Metabolism.—The authors report three cases of this syndrome, which is different from the cases Lightwood and other English writers have described; the severe form does not clear up as the milder one does. All three infants showed growth failure, persistent hypercalcemia, normal or elevated phosphatemia, renal disturbances, hypercalciuria and hyperphosphaturia, osteosclerosis, slightly lowered alkali reserve, and normal chloride and sodium. Two of three showed slight elevation of cholesterol and two had asymptomatic heart disease. Vomiting is common. Two of the three appeared mentally retarded (one of them had microcrania). Renal impairment was present in all three. Azotemia was present in all three. Results of tests for glomerular filtration, renal plasma flow, and tubular secretory function indicated impairment and were consistent with a loss of total nephron population. A renal biopsy in one case revealed atrophy of cortex and tubules. Serum bioassays for vitamin D revealed activity 20-30 times that of a normal infant getting the usual amount of vitamin D. Vitamin A levels were elevated in all three infants. Balance studies indicated a marked retention of calcium. This was felt to contribute to the osteosclerosis that is present in spite of the hypercalciuria. Nitrogen retention was negligible.

The authors mention the work of others who found abnormal elevations of beta lipoprotein and suggested that a defect in cholesterol metabolism was present. The authors felt that their studies demonstrated a defect in metabolism of vitamin D.

News and Comment

ANNOUNCEMENTS

International Congress for Internal Medicine.—The Sixth International Congress for Internal Medicine will be held in Basel, Switzerland, from August 24 to 27, 1960. This Congress will be organized in conjunction with the Swiss Society for Internal Medicine. For further details apply to the Secretariat of the Sixth International Congress for Internal Medicine, 13, Steinentorstr., Basel.

Conference on Mental Retardation.—The First International Conference on Mental Retardation will be held July 27-31, 1959, at the Eastland Hotel, Portland, Maine.

Registration can be accomplished by writing to International Medical Conference on Mental Retardation, c/o Division of Maternal and Child Health, State House, Augusta, Maine. A varied program will be presented. The speakers will be as follows: P. I. Yakovlev (Boston), E. Gellhorn (Minneapolis), D. Y. Hsia (Chicago), J. D. Spillane (Cardiff), W. F. Ingram (Iowa City), R. S. Paine (Boston), P. B. Diezel (Heidelberg), J. N. Cumings (London), H. Bickel (Marburg), J. Wortis (Brooklyn), P. Schwartz (Warren, Pa.), L. S. James (New York), J. Warkany (Cincinnati), H. Asperger (Innsbruck), M. Schachter (Marseilles), B. Pasamanick (Columbus, Ohio), C. E. Benda (Waverly, Mass.), W. W. Zuelzer (Detroit), K. Kundratitz (Vienna), J. Oester (Randers, Denmark), H. S. Barr (Pownal, Maine), P. H. Gates (Boston), G. E. Gardner (Boston).

Instrument Symposium and Research Equipment Exhibit.—The Ninth Annual Instrument Symposium and Research Equipment Exhibit will be held Sept. 28 through Oct. 1, 1959, at the National Institutes of Health Bethesda, Md.

Sponsors of the exhibit are the nation's leading instrument manufacturers, who will display the newest developments in laboratory glassware and electronic, surgical, radiation, optical, gas-sampling, and other research equipment.

Sponsors of the symposium are the Washington, D. C., sections of the American Association of Clinical Chemists, American Chemical Society, Instrument Society of America, Professional Group on Medical Electronics of the Institute of Radio Engineers, Society of American Bacteriologists, and the Society for Experimental Biology and Medicine.

For additional information about the symposium and exhibit, write or call James B. Davis, National Institutes of Health, Public Health Service, Bethesda 14, Md. Phone: OLiver 6-4000, extension 2315.

Summer Clinics at Denver Children's Hospital.—The 11th Annual Summer Clinics of the Denver Children's Hospital will be held June 24, 25, and 26, 1959. Guest faculty to augment the Medical Staff and local teachers includes J. Roswell Gallagher, M.D., Chief of the Adolescent Unit, Boston Children's Hospital; F. Howell Wright, M.D., Professor and Chairman of the Department of Pediatrics, University of Chicago School of Medicine, and Judge Leo B. Blessing, LL.D., Judge of the Juvenile Court, New Orleans. In addition to a series of small-group round tables on recent developments applicable to general pediatric care, serious attention will be directed to the social—and medical—problems the teenager must adjust to, or overcome, before finding acceptable status in the community. The increasing frequency with which the physician is called upon by perplexed parents, school authorities, law enforcement agencies, and civic groups for authoritative advice makes this year's program most timely. Cost of the course, including luncheons and banquet, remains at $35.00. Further information may be secured by addressing the Chairman, Summer Clinics Committee, Children's Hospital, Denver 18.

Traineeships in Cardiovascular Research.—Traineeships in Cardiovascular Research are available for qualified persons at the Childrens Hospital of Los Angeles. Appointments may be made either in clinical pediatric cardiology or in pertinent basic sciences. Appointments are made for one year and may be extended to two or three years. First year clinical trainees spend most of their time attaining the requisite skills in pediatric cardiology, although they may participate in selected clinical studies under supervision. Second-year clinical trainees continue their clinical training, assuming greater responsibility, and spend up to half time in

supervised research activity with increasing independence. Third-year trainees spend the majority of time in research while maintaining close contact with clinical activities. Teaching activities and responsibilities are scaled accordingly.

These traineeships, both clinical and basic science, are designed primarily for those interested in the possibility of a career in research and teaching in pediatric cardiology and related disciplines.

The institutional facilities are excellent and the clinical material extensive. All ancillary services are exceptional, and the training program is well staffed. Applications are invited. Further information is available on request.

Residency in Rehabilitation.—Applications are now being received for three- to six-month residencies in Pediatric Rehabilitation at the Jewish Chronic Disease Hospital, Brooklyn. Residents are given an opportunity to gain experience in the rehabilitation approach to the chronic diseases of children, including the neuromuscular diseases, such as poliomyelitis, spina bifida, muscular dystrophy; visceral handicaps, such as congenital heart disease and cleft palate, and to a variety of communication and psychologic handicaps. The service is a teaching unit of the State of New York Medical School and is fully staffed and fully equiped for this type of work. There will also be experience in cardiac catheterization, angiocardiography, and an opportunity to observe patients undergoing cardiological operations.

The stipend is $200 a month. Applicants receiving their pediatric training in an accredited institution will receive three months of credit toward certification by the American Board of Pediatrics. Vacancies are now open, beginning July 1, 1959.

Applications should be sent to Director of Pediatrics, E. 49th St. and Rutland Rd., Brooklyn 3, N. Y.

GENERAL NEWS

Specialists Certified in Pediatric Allergy.—The following pediatricians were certified in the subspecialty of Pediatric Allergy by the American Board of Pediatrics, Inc., on Feb. 8, 1959, in Chicago:

Daniel Blitz, Woodmere, N. Y.
John Gerard Flynn, Salem, Mass.
John S. Hyde, Oak Park, Ill.
Raymond W. Latham, Kansas City, Mo.
Richard Lawrence London, Rochester, N. Y.
Lloyd Stanley Nelson, Minneapolis 2.
Ronald Reuben, Beverly Hills, Calif.
Alexander Roth, Prairie Village, Kan.
Edward Louis Strem, St. Paul.

New Research Center in District of Columbia.—On Sunday, March 22, Children's Hospital of the District of Columbia dedicated its new Children's Hospital Variety Club Research Center. Dedication speaker was Dr. Leroy E. Burney, Surgeon General of the United States Public Health Service.

The Research Center, located next to the Hospital, at 12th and W Streets, N. W., was built at a cost of approximately $800,000. This was financed in part by grants totaling $484,000 and by a contribution of $200,000 from the Variety Club of Washington. Additional funds are being raised in a campaign for $460,000 which was launched by Children's Hospital last November. This campaign is part of an over-all building and modernization program for the Hospital costing $1,117,357. By March 1, 600 contributors had subscribed in excess of $300,000 leaving a goal of $160,000 still to be reached.

The Children's Hospital Variety Club Research Center, which commemorates the Variety Club's former Chief Barker, Fred S. Kogod, is a modern building with three floors and a basement. The front is of heavy, opaque glass and aluminum, and the sides are of brick to complement existing hospital buildings.

In the air-conditioned building all necessary services (water, electricity, gas, compressed air) will be available in each research unit. Movable partitions will allow rearrangement of research areas without extensive repairs and remodeling. In addition to the laboratories of the seven research sections there is a radioisotope laboratory and a large sterilizing room with the latest equipment for washing and sterilizing all glassware used in the laboratories.

The Research Foundation of Children's Hospital was incorporated in 1947 to further pediatric research at Children's Hospital. Its President is Dr. Edgar W. Davis, and the Director of the Foundation is Dr. Robert H. Parrott, Physician-in-Chief of Children's Hospital.

Supported in part by grants from the government, leading pharmaceutical companies, and national research organizations, the Research Foundation of Children's Hospital has undertaken important research projects since its inception. In reckoning the tangible dividends of its

research the Foundation can point with pride to one of its first projects—the diarrhea control study. Ten years ago, when the Foundation was in its infancy, 15 out of every 100 infants hospitalized with diarrhea lost their lives. As the result of the studies undertaken by the Research Foundation, out of which evolved a procedure for treatment, the recovery rate of these patients today is 99 out of 100.

In the past year the Virology Section of the Research Foundation co-hosted, with the Georgetown University School of Medicine's Department of Pediatrics, a conference on Pediatric Virology, which was attended by physicians and researchers from many parts of the United States. In collaboration with the National Institutes of Health the Virology Section of the Foundation isolated, by means of the hemadsorption technique, two new viruses which have been causing serious respiratory illnesses in children. In its continuing studies the Virology Section of the Research Foundation is striving to relate newly discovered viruses to clinical diseases.

The Microbiology Section carries on a constant war on the Staphylococcus aureus. This research group has been keeping this organism under close surveillance for many years, and work is being planned to investigate protective measures against this hospital invader. The Microbiology Section also carries on evaluation of new antibiotic drugs.

The major activity of the Hematology Section of the Research Foundation is devoted to the study of the white cells of infants and children, in the hope of arriving at a better understanding of the cause of leukemia and of obtaining methods for its prevention and treatment. Although the concentration of the Hematology Section is in the field of leukemia, various anemias and abnormal hemaglobins are also under study.

The Psychiatry Section of the Research Foundation of Children's Hospital was prominent last year in planning and carrying out a national meeting of psychiatrists concerned with the use of tranquilizing drugs in children. In its new laboratories in the Research Center this Section will take advantage of the one-way glass partitioning the playroom from the laboratory to observe emotionally disturbed children, and to undertake research on pica—an abnormal appetite for substances not fit for food.

In addition to its Pediatric Allergy Fellowship Training Program in the fundamentals of immunology and hypersensitivity, the Allergy Section is undertaking research in the use of gamma globulin in the treatment of asthma. Other important research projects of the Allergy Section concern the allergenicity of corn products, and the nutritional and hypoallergic properties of a new soybean formula for infants.

The Renal Section of the Research Foundation is training physicians in the diagnosis and treatment of kidney diseases, and is conducting research in virus diseases of the kidney.

A laboratory for the Metabolic Diseases Section has been allocated in the new building, and the Section will be activated in the near future.

In 1958 the staff of the Research Foundation of Children's Hospital prepared more than 10 papers in conjunction with their research. Two of these concerned the clinical manifestations of Asian influenza, and the nature and treatment of acetylsalicylic acid (aspirin) poisoning.

In its new quarters in the Children's Hospital Variety Club Research Center the Research Foundation will continue to attract a top-ranking staff, and will be able to meet the full needs of the community which it serves. In the words of Dr. William S. Anderson, Chairman of the Medical Staff of the Hospital, "Every child who comes to Children's Hospital will benefit either directly or indirectly from its medical research program." Even more, as the benefits of medical research reach out across the nation and to other lands, the Children's Hospital Variety Club Research Center will have a great effect on the lives of untold numbers of children and their families.

$750,000 Given by Markle Fund to Aid Medical School Faculties.—Twenty-five physicians, teachers, and research workers on the faculties of medical schools in the United States and Canada have been appointed Markle Scholars in Medical Science by the John and Mary R. Markle Foundation, New York. Each appointment carries with it a $30,000 grant, appropriated to the medical school where the Scholar will teach and do research, to be used toward his support and to aid his research.

In the 12 years the fund has been making the Scholar grants, over 250 doctors in 74 medical schools in the United States and Canada have been aided with total appropriations of $7,550,000. John M. Russell, executive director and vice-president of the fund, said, "The purpose of the program is 'to strengthen medical education by offering academic security and financial help to teachers and investigators in medical schools early in their careers'."

There were more applicants for the grants this year than ever before, Mr. Russell said. The 25 Scholars were selected from nominees from 65 medical schools by five committees of educators and other professional men through extended interviews over three-day periods.

The John and Mary R. Markle Foundation was estaablished in 1927 by the late John Markle, Pennsylvania coal operator, "to promote the advancement and diffusion of knowledge . . . and the general good of mankind." The Scholar in Medical Science program, the present major interest of the fund, began in 1948.

The 25 Markle Scholars in Medical Science whose appointments begin in 1959, their fields of interest, and the medical schools that will receive $30,000 grants toward their support for the five years, 1959-1964, are as follows:

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST. LOUIS, *for* BRUCE M. BRECKENRIDGE, Ph.D., M.D., instructor. (B.S., Iowa State College; M.S., Ph.D., M.D., University of Rochester) Pharmacology

COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, New York, *for* CHARLES L. CHRISTIAN, M.D., instructor. (B.A., University of Wichita; M.D., Western Reserve University) Internal medicine

WAYNE STATE COLLEGE OF MEDICINE, Detroit, *for* GEORGE O. CLIFFORD, M.D., assistant professor. (Undergraduate, Harvard College; M.D., Tufts University) Internal medicine

UNIVERSITY OF MIAMI SCHOOL OF MEDICINE, Coral Gables, Fla., *for* N. JOEL EHRENKRANZ, M.D., assistant professor. (B.S., Sheffield Scientific School, Yale University; M.D., Yale University) Internal medicine

UNIVERSITY OF CHICAGO DIVISION OF THE BIOLOGICAL SCIENCES, Chicago, *for* CLIFFORD W. GURNEY, M.D., assistant professor. (B.S., M.D., University of Chicago) Internal medicine

UNIVERSITY OF UTAH COLLEGE OF MEDICINE, Salt Lake City, *for* ARTHUR HAUT, M.D., instructor. (A.B., M.D., Columbia University) Internal medicine

WESTERN RESERVE UNIVERSITY SCHOOL OF MEDICINE, Cleveland, *for* CARL F. HINZ JR., M.D., instructor. (B.S., M.D., Western Reserve University) Internal medicine

YALE UNIVERSITY SCHOOL OF MEDICINE, New Haven, Conn., *for* MICHAEL HUME, M.D., instructor. (B.A., Yale University; M.D., Columbia University) Surgery

UNIVERSITY OF MONTREAL FACULTY OF MEDICINE, Montreal, Canada, *for* GUY LEMIEUX, M.D., instructor, effective July 1; currently, graduate medical research fellow, National Research Council of Canada; Tufts University School of Medicine, Boston (B.A., M.D., University of Montreal) Internal medicine

UNIVERSITY OF VERMONT COLLEGE OF MEDICINE, Burlington, Vt. *for* JEROLD F. LUCEY, M.D., assistant professor, effective July 1. (A.B., Dartmouth College; M.D., New York University) Pediatrics

VANDERBILT UNIVERSITY SCHOOL OF MEDICINE, Nashville, Tenn. *for* ERNEST E. MCCOY, M.D., instructor. (B.Sc., M.D., University of Alberta) Pediatrics

JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, Baltimore, *for* GERARD B. ODELL, M.D., instructor. (B.A., New York University; M.D., Yale University) Pediatrics

UNIVERSITY OF COLORADO SCHOOL OF MEDICINE, Denver, *for* MARSHALL J. ORLOFF, M.D., assistant professor. (B.S., M.S., M.D., University of Illinois) Surgery

DUKE UNIVERSITY SCHOOL OF MEDICINE, Durham, N. C. *for* SUYDAM OSTERHOUT, M.D., associate in medicine; currently, graduate fellow, Rockefeller Institute, New York. (B.A., Princeton University; M.D., Duke University) Internal medicine

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE, Pittsburgh, *for* BARRY PIERCE, M.D., assistant professor. (M.Sc., M.D., University of Alberta) Pathology

UNIVERSITY OF WISCONSIN MEDICAL SCHOOL, Madison, Wis. *for* JOHN RANKIN, M.D., assistant professor. (M.B., Ch.B., University of Glasgow; M.D., University of Wisconsin) Internal medicine

STATE UNIVERSITY OF NEW YORK DOWNSTATE MEDICAL CENTER COLLEGE OF MEDICINE, Brooklyn, *for* PHILIP N. SAWYER, M.D., instructor. (Undergraduate, Harvard College; M.D., University of Pennsylvania) Surgery

MCGILL UNIVERSITY FACULTY OF MEDICINE, Montreal, *for* HUNTINGTON SHELDON, M.D., assistant professor, effective July 1; currently, instructor and fellow; Johns Hopkins University School of Medicine. (B.A., McGill University; M.D., Johns Hopkins University) Pathology

NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, Chicago, *for* THOMAS E. STARZL, Ph.D., M.D., instructor, effective July 1; currently resident. (B.A., Westminster College; M.A., Ph.D., M.D., Northwestern University) Surgery

UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE, Seattle, *for* AUGUST G. SWANSON, M.D., instructor. (A.B., Westminster College; M.D., Harvard University) Neurology

TULANE UNIVERSITY SCHOOL OF MEDICINE, New Orleans, *for* WILLIAM G. THURMAN, M.D., instructor. (B.S., University of North Carolina; M.D., McGill University) Pediatrics

UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE, Louisville, Ky. *for* ARTHUR C. WHITE, M.D., instructor (B.S., University of Kentucky; M.D., Harvard University) Internal medicine

UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE, Philadelphia, *for* ALBERT I. WINEGRAD, M.D., associate in medicine. (Undergraduate, M.D., University of Pennsylvania) Internal medicine

HARVARD MEDICAL SCHOOL, Boston, *for* F. EUGENE YATES, M.D., associate. (B.A., M.D., Stanford University) Physiology

UNIVERSITY OF NORTH CAROLINA SCHOOL OF MEDICINE, Chapel Hill, N. C. *for* ROBERT ZEPPA, M.D., instructor. (A.B., Columbia College; M.D., Yale University) Surgery

Specialists Certified by the American Board of Pediatrics, Inc.—The following physicians were certified as specialist by the American Board of Pediatrics, Inc., in New Orleans, on March 6, 7, and 8, 1959.

Angulo, Edilberto D., Lansing, Ill.
Appelboom, Johannes W. Th., Lyndon, Ky.
Bargeron, L. M. Jr., Birmingham, Ala.
Barkin, Gilbert Donald, Houston, Texas.
Bartlett, William Herbert, Madison, Wis.
Bell, Emmett D. Jr., Memphis, Tenn.
Brice, George W. Jr., Charlotte, N. C.
Bridges, William Lee Jr., Tifton, Ga.
Brous, Marion Wilson, Fort Worth, Texas.
Cersonsky, H. Sol, Aurora, Colo.
Chambers, David Conrad, Los Angeles.
Combes, Mollie Allensworth, Dallas, Texas.
Corpening, Joseph Durham, Salisbury, N. C.
Crandall, Homer L., Birmingham, Ala.
Dell, George Alexander, Gainesville, Fla.
Doss, Wilford Cleve Jr., Florence, Ala.
Drewry, David Barnes, Petersburg, Va.
Ellenbogen, Nina Claire, Miami Beach, Fla.
Erwin, George, Athens, Ga.
Fink, Chester Walter, Dallas, Texas.
French, John David, Martinsville, Va.
Goldfarb, Irvin Joseph, El Paso, Texas.
Graziani, Angel M. Romero, Hato Rey, Puerto Rico.
Greiwe, Thomas Hoppe, Tampa, Fla.
Grover, Frederick Wilson, Dallas, Texas.
Halden, William Joseph, Austin, Texas.
Indenbaum, Joseph K., Los Angeles, Calif.
James, Charles Alston, Randolph Air Force Base, Texas.
Jelliffe, Derrick Brian, Uganda, East Africa.
Johnson, Benjamin Allen, Jacksonville, Fla.
Kay, Jacob Lindy, Houston, Texas.
Kepler, Milton Oliver, Fayetteville, New York.
Keyes, Robert C., Fort Wayne, Ind.
Kraus, Michael, Chicago.
Lahser, Charles I., Gastonia, N. C.
Lancaster, James William, Coral Gables, Fla.
Lawlis, Marjorie Grover, Austin, Texas.
Liebes, George J., Dallas, Texas.
Luecke, Percy E. Jr., Dallas, Texas.
Lugg, Robert Milton, Port Huron, Mich.
Martin, Gladys E. O., Dickinson, N. D.
Mathis, Edwin F., Little Rock, Ark.
Nambu, Albert T., Torrance, Calif.
O'Brien, Donough, Denver.
O'Connor, Patricia Ann, Little Rock, Ark.
Ongley, Patrick Augustine, Rochester, Minn.
Palcheff, Chris Lazar, Springfield, Mo.
Phelps, Patsy Ruth, Raceland, La.
Plunket, Daniel C., San Francisco.
Porter, F. Stanley, Little Rock, Ark.
Ray, Esten Williams, Syracuse, N. Y.
Reid, John Harris, Flint, Mich.
Rolfes, Leonard J., Lafayette, La.
Salhanick, Catherine Orr, Omaha.
Santiago, Rafael Blasini, Ponce, Puerto Rico.
Schroeder, Robert Walter, Marion, Ind.
Sellars, William A., Dallas, Texas.
Stewart, Gloria Ann, New Orleans.
Strominger, Donald B., Wiesbaden, Germany.
Vandever, Harry Wallace, Oklahoma City.
Vietti, Teresa Jane, Dallas, Texas.
Waddell, Pearl Boulware, Fort Smith, Ark.
Walker, William A., Decatur, Ala.
Warren, Philip, Waterbury, Conn.
Weller, Fred Burnam, Middlesboro, Ky.
White, Dewey, A. Jr., Birmingham, Ala.
Worsham, A. Gordon, Dallas, Texas.
Wray, Joe David, Ankara, Turkey.
Zeliff, John E., Greenville, S. C.

Special Foreign Certificate

Trevino, Carlos Perez, Corpus Christi, Texas.

National Foundation Research Grants.—The National Foundation on Feb. 21 announced 20 research grants reflecting the new attack on arthritis, birth defects, and intensified scientific investigation of viruses.

Totaling $1,256,232 in March of Dimes funds, the awards launch the National Foundation's expanded health research program for 1959, according to its president, Basil O'Connor.

The puzzle of how the rheumatic diseases cause tissue damage will be investigated at three institutions under newly approved grants. Although little is known about what causes rheumatoid arthritis, the most serious of the rheumatic diseases, scientists suspect that allergy reactions, abnormal antibodies, and other blood factors may play a significant part in the disease. These possibilities will be studied.

Following is a list of National Foundation research grants announced today:

University of Michigan, Ann Arbor, Mich.: $144,010 to seek chemical compounds or drugs against polio and other viruses; to study how viruses and living cells act on each other, and to investigate polio incidence in respect to the effectiveness of Salk vaccinations.

University of Utah, Salt Lake City: $53,560 to study what happens when a virus invades a cell, particularly in respect to cellular enzyme and nucleic acid activity.

Washington University, St. Louis: $22,244 to study the central nervous system in an attempt to learn why some cells are vulnerable to polio virus attack and others are not.

California Institute of Technology, Pasadena, Calif.: $73,594 to conduct basic studies of heredity in viruses, and to begin studies of the chemistry of virus nucleic acid production.

Columbia University, New York: $53,923 to study how viruses multiply and cause damage to the cells they infect.

Columbia University, New York: $55,814 to study heredity in polio viruses and relationships between polio viruses and other polio-like enteroviruses.

University of Chicago, Chicago: $73,866 to study what happens chemically when bacterial viruses infect host bacteria and when polio viruses infect cancer cells, in an attempt to learn more about how viruses operate.

St. Louis University, St. Louis: $15,414 to conduct basic research on the part played by protein in the reproduction and growth of viruses.

The Rockefeller Institute, New York: $52,965 to carry out basic research on virus heredity, using bacterial viruses in an attempt to learn if nucleic acid alone is responsible for transferring hereditary characteristics or if viral protein also plays a part.

University of Cincinnati, Cincinnati: $116,400 to coordinate and analyze field tests of live virus polio vaccine, and to investigate the problems of a number of viruses other than polio, some of which may be responsible for common wintertime respiratory illnesses.

Tulane University, New Orleans: $90,641 to continue studies of the effects of vaccination against polio with both Salk and live-virus vaccines; and to classify collected samples of intestinal viruses other than polio virus.

The Mount Sinai Hospital, New York: $31,665 to continue attempts to perfect a simple and effective test for the presence or absence in the blood of polio antibodies, and for studies to trace the paths followed by polio virus from the time it enters the body until the disease has run its course.

Western Reserve University, Cleveland: $49,325 to continue studies of enteroviruses as possible causes of aseptic meningitis and to investigate certain unusual antibody effects on virus growth.

University of Buffalo, Buffalo: $21,914 for continued study of aseptic meningitis in hospitalized children caused by ECHO and Coxsackie viruses and for investigations of certain ECHO virus variants.

New York University-Bellevue Medical Center, New York: $61,969 for basic research on how rheumatic diseases cause tissue damage.

University of Buffalo, Buffalo: $143,185 to study the possible role of autoantibodies in rheumatoid arthritis and other connective tissue diseases.

Vanderbilt University, Nashville, Tenn.: $43,790 to investigate the significance of certain antibody mechanisms in the tissue damage that occurs with rheumatoid arthritis and other connective tissue disorders.

California Institute of Technology, Pasadena, Calif.: $33,943 to continue attempts to determine the precise molecular structure of certain viral nucleic acids.

University of Saskatchewan, Saskatoon, Canada: $68,010 for investigations of the possible part played by body fats in infections by viruses that attack nervous tissues.

Protein Foundation, Inc., Boston: $50,000 to investigate the role of certain normal and abnormal blood components in relation to arthritis.

Books

BOOK REVIEWS

Medulloblastoma. By Lt. Comdr. Benjamin L. Crue Jr. (MC) U. S. N. Price, $5.75. Pp. 206, with 16 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

The present monograph deals with the origin, location, structure, symptoms, and treatment of one pathological entity, namely, medulloblastoma.

After reviewing the known causes of malignancy, the author inclines toward the theory that medulloblastoma is a congenital tumor arising from cell rests. The medulloblast has bipotential properties and may give rise to either glial or neuronal cells. The evidence is strongly suggestive that the retained medulloblasts giving rise to the tumor are similar to those of the external granular layer of the cerebellum, acting as true cell rests.

The medulloblastoma is a midline, cerebellar tumor. According to the writer, the question of the presence of a rare case of cerebral medulloblastoma is not settled. There may be some relationship of medulloblastoma to the neuroectodermal tumors such as neuroblastoma or oligodendroglioma. It may also shade into the group of rare intracranial sarcomas. The classification is not agreed upon at present; hence, statistics must be interpreted according to the definitions used. In this presentation, only tumors which occur in the posterior fossa (subtentorial) are included under "medulloblastoma." Metastatic and cerebral tumors are eliminated. Twenty-five per cent of all brain tumors in children are medulloblastomas. They occur twice as often in males, and more frequently in the age group of 3 to 10 years.

While the title of this monograph is medulloblastoma, which to pediatricians may appear to be too limited in scope, the subject matter is of a much wider range. The chapter on general considerations of neoplasia is a fine, succinct review of the present theories as to the cause of cancer. Throughout the text are interspersed excellent comments, such as the need to register the spinal fluid pressure by means of a manometer, rather than to observe that the spinal fluid spurts out of the needle. There is emphatic stress placed upon the need to explore every suspected tumor, rather than to assume it to be a medulloblastoma and hence fatal. A curable hemangioma or slow growing astrocytoma may be revealed. Early surgery may avoid blindness, when a benign tumor is discovered.

Further research is indicated utilizing clinical experimentation with hormones and laboratory studies with tissue cultures, tumor transplants, and tumor production.

Interesting chapters on symptoms and signs, differential diagnosis, and treatment, and an extensive bibliography add to the enjoyment and value of the book.

STANLEY S. LAMM, M.D.

The Nursing Mother. By Frank Howard Richardson. Price, not given. Tupper and Love, 55 5th Ave., New York 3, 1958.

As Dr. Richardson emphasizes, infants should be breast-fed up to the age of six months if possible because human milk is the best milk for young infants. It has preventive and therapeutic value and is economical, easily digestible, fresh, free from contamination, automatically produced, and time-saving. It is the safest food for premature infants who are mature enough to suckle at the breast. Instances of breast milk "not aggreeing with an infant" are almost unknown. Breast feeding provides gratification and a sense of security to babies. Breast feeding also is important physiologically and psychologically to mothers.

The only contraindications to breast feeding are heart, kidney, lung, and psychiatric diseases in the mother. Also, she should not take drugs which pass into her milk, e. g., antibiotics atropine, barbiturates, bromides, iodides, morphine, salicylates, and sulfonamides.

Most mothers can nurse their infants if they have the desire, proper pre- and postnatal care, adequate sleep, moderate exercise, freedom from worry, and a good pre- and postnatal diet. They should drink one quart of milk and an additional quart of fluid daily and eat fruit, salads, green vegetables, eggs, meat, cod liver oil or its equivalent, and whole wheat bread in three to four well-balanced meals and rest at least one hour daily in addition to eight hours at night.

Normal infants suckle and swallow at birth; inability to nurse well is more likely to be due to an imperfect central nervous system than to muscular weakness, except in premature infants.

This book is highly recommended to general practitioners, obstetricians, and pediatricians.

W. C. DAVISON

Bibliography of Internal Medicine: Communicable Diseases. Edited by Arthur L. Bloomfield, M.D. Price, $10.00. Pp. 537. The University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1958.

This volume represents a selected bibliography of communicable diseases involving the most important contributions of the literature made to each of 30 such diseases during the past 160 years. This bibliography is eminently readable, although its main purpose may well be that of a reference for medical students and their teachers. Dr. Bloomfield, who is now Professor Emeritus of Medicine at Stanford University School of Medicine, has previously published some of the sections of this bibliography in a number of medical journals, including the *A. M. A. Archives of Internal Medicine* and the *Journal of Chronic Diseases*. Dr. Bloomfield was clearly motivated by his truly passionate desire to prevent a final isolation of the modern student and practitioner from his medical heritage. The important contributions of medicine in the 19th and 20th centuries have such an important bearing on the development of recent ideas and concepts in modern medicine that our ignorance of even the most important of such contributions represents a serious deficiency. "The surge of new knowledge in medicine has created a tremendous problem. The student tends to keep up on the new, the curious, and the esoteric at the expense of the fundamental and the historical. In current medical writing, what is referred to as the 'older literature' often turns out to be that of the previous decade. In brief, there is a real danger that we shall become completely cut off from our medical past and will lapse into a sort of modern dark age."

Dr. Bloomfield's bibliography takes us through the gamut of infectious diseases and provides for each some 30 to 40 references which are clearly analyzed as to scope and value. In reading them one becomes delightfully aware of the indebtedness of one generation of medical scientists to those who precede them, and at the same time one is struck by the frequency with which major observations are arrived at independently at approximately the same time by diverse individuals. Although the abstracts are eminently readable and critically evaluated with a refreshingly youthful point of view which reflects Dr. Bloomfield's personal wisdom and sense of excellence, this book is perhaps best sampled. It is uniquely suitable for short snatches of reading at frequent intervals and is a gold mine of information at once instructive and enjoyable.

Because of the uniqueness of this approach, Dr. Bloomfield is to be congratulated on a successful experiment to bring medical science of the past to bear on medical science of the future.

C. Henry Kempe, M.D.

Handbook of Treatment of Acute Poisoning. By E. H. Bensley, M.B.E., B.A., M.D., F.A.C.P., and G. E. Joron, B.A., M.D., C.M., F.A.C.P. Price, $4.00. Pp. 212. E. & S. Livingstone, Ltd., 16 and 17 Teviot Place, Edinburgh 1 (American agent—The Williams & Wilkins Company, Mount Royal & Guilford Aves., Baltimore 2), 1958.

The authors set out to write a monograph of limited scope that will encompass two objectives: to impart certain general principles in the treatment of acute poisoning, and to provide a convenient reference source of the clinical manifestations and treatments of the common types of poisoning. Toward the second objective the book is admirably well written and organized. Forty-eight general classes of poisoning are discussed in an alphabetical sequence which also appears in the table of contents, making speedy reference to any one topic a relatively easy task. Under each topic, various related toxic substances, their lay names, and certain household articles in which they appear are given; also presented in each topic are the symptomatology of poisoning, emergency measures of treatment, specific therapy wherever possible, and, lastly, management of the after-effects wherever necessary. In addition, a good index is available so that reference to any specific toxic substance can be made.

The monograph incorporates many recent advances in the specific therapy of certain types of poisoning, such as the use of newer respiratory stimulants in barbiturate and in morphine poisoning, the medical use of chelating agents, the treatment of fluoroacetate poisoning, and the therapy of poisoning caused by newer insecticides. In this respect, the monograph will serve as an invaluable aid to the practitioner who has only an occasional contact with acute poisoning and who may wish to keep abreast with and make use of recent developments. Toward the first objective of imparting certain general principles in the treatment of acute poisoning, however, the authors have done little more than to provide a few useful empirical formulations, which, to be sure, are derived from a wealth of experience, and which may be advantageously adopted by other practitioners as well. Nevertheless, the main deficiency of

this monograph lies in the generally superficial and sometimes erroneous rendition of the basic pharmacological actions of the poisons or therapeutic agents. In spite of the avowedly limited scope of this book, much improvement could be made in this respect without lengthening the book itself. Indeed, a volume twice the size of this monograph, including some of the rarer types of poisoning, will still be a useful and welcomed aid to the practitioner, because it is for some of the uncommon poisonings that he would need a handy reference.

C. Y. Kao

Cleft Palate and Speech. Fourth Edition. By Muriel E. Morley, M.Sc., F.C.S.T. Price, $6.50. Pp. 270, with 80 illustrations. E. & S. Livingstone, Ltd., 16 and 17 Teviot Place, Edinburgh ' American agent—The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2), 1958.

This fourth edition of Miss Morley's splendid book contains a very specialized wealth of information on the child with a cleft palate—a veritable encyclopedia in miniature.

While the book has been directed mainly toward plastic surgeons and speech therapists, it contains detailed and accurate sections on the following: The Embryology of the Central Face; Normal and Pathologic Physiology of the Lips, Jaws, Palate and Pharynx; Growth Patterns; Feeding Problems; Surgical Methods of Repair; Factors Influencing Speech; and a detailed and illuminating section on the "Total Treatment of the Child With a Cleft Palate."

The plastic surgeon's goal for the child with a cleft palate is to produce normal, natural speech and good physical appearance. Normal speech is defined as that which is intelligible, natural, free from defects and equal to that of his contemporaries.

The optimum time to repair clefts of the lip is 4 to 8 weeks of age, or when the child reaches 10 lb. in weight. The optimum time to reconstruct clefts of the palate is approximately 16-18 months of age, or when the child begins to talk. If the requirements for natural speech are not provided early in life, and the child reaches the age when he is aware that others regard his speech as defective, lack of confidence in what should be an easy and unconscious means of expressing his thoughts may never be entirely eradicated.

The best efforts of the most expert speech therapist will be of little avail if the palate has been ruined by ill-planned or poorly executed surgical procedures.

Miss Morley's book cements the relationship and association between the plastic surgeon, the speech therapist, and the orthodontist. It enables each to understand, complement, and augment the work of each member of the team. She has imparted to all of us the knowledge gained by years of close association with a number of England's outstanding plastic surgeons.

The book is recommended highly for plastic surgeons, speech therapists, and orthodontists. It is an invaluable reference aid for pediatricians, child psychologists, and dentists. The price of the book is $6.50. The volumn is small enough to fit into one's coat pocket.

Kenneth L. Pickrell, M.D.

Difficult Diagnosis: A Guide to the Interpretation of Obscure Illness. By H. J. Roberts, M.D. Price, $19. Pp. 913, with 99 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

This is a prodigious undertaking for a practicing internist. However, he has successfully woven in a vast clinical experience with current knowledge to present a well-organized, concise, yet informative, discussion of difficult diagnoses. An important aid is Part II, entitled "A Classification and Analysis of Useful Diagnostic Procedures." The value of the text is enhanced further by an extensive bibliography and an index of signs, symptoms, and laboratory manifestations. The chapter on Cutaneous Medicine is well illustrated with an atlas of 99 pictures. An increasingly important subject is well presented in the chapter entitled "Iatrogenic Illness."

This book will serve as a valuable addition to the library of both internists and general practitioners.

William J. A. DeMaria, M.D.

Emotional Problems of Childhood. Edited by Samuel Liebman, M.D. Price, $5. Pp. 176, with 2 illustrations. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 6, 1958.

Two of the physician's most challenging problems are the recognition of when behavior leaves the fringe of normal and becomes abnormal and the early management best suited to the condition. The collection of lectures comprising this book serves this area well. Basic information and dynamics are presented with clear examples and interpretations aiding greatly

the understanding and beginning management of, for example, feeding problems in infancy, speech problems in children, common problems in adolescence, and the problems of the physically handicapped child.

This book is highly recommended for the pediatrician, the general practitioner, and the internist who is physician to the adolescent.

WILLIAM J. A. DEMARIA, M.D.

Discussions on Child Development. Volume Three. Edited by J. M. Tanner, M.D., D.Sc., D.P.M., and B. Infelder. Price, $5. Pp. 223, with 19 illustrations. International Universities Press, Inc., 227 W. 13th St., New York 11, 1958.

Physical and Behavioral Growth. Report of the Twenty-Sixth Ross Pediatric Research Conference. Price, not given. Pp. 101, with 15 illustrations. Ross Laboratories, Columbus 16, Ohio, 1958.

A previous review in this Journal described volumes 1 and 2 of the discussions on Child Development. The publication of the third volume adds to the knowledge and satisfaction to be gained from following these erudite discourses. Those interested in this method of presentation of knowledge about children and their growth will also be pleased with the publication of the Ross Conference on Growth.

Of special interest in the WHO volume are the studies of Margaret Mead on sex differentiation and those of Erik Erikson on the adolescent's problem in finding his identity. Dr. Mead's contribution reflects the common concern over differentials in the manner in which the two sexes are reared. Her evidence concerning such environmental differences is most full and suggests important conclusions for further studies.

Those who are aware of Mr. Erikson's masterful contributions to a full understanding of growth will welcome his newer statements on the period of adolescence. The usually stimulating and highly erudite discussion of these papers continues to make the volume series worth while.

It is good to see in the Ross Conference report another American attempt to augment this type of interdisciplinary discussion. Pediatric readers will find a range of articles from Infancy to Adolescence. The presentations are briefer than those of the WHO volume, and there may be too much range. However, the discussion seemed fruitful and one wishes that more of the latter had been published. HENRY H. WORK, M.D.

Modern Trends in Pediatrics. Edited by A. Holzel and J. P. M. Tizard. Price, not given. Pp. 372. Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 43 E. 33d St., New York 16, 1958.

The editors of this collection of essays state that "the authors have been asked only to discuss matters which they consider to be important and in which they have special interest, since we believe that a text-book which tries to cover its subjects completely often loses more in authority than it gains in comprehensiveness." This is excellent advice. It should be followed by everyone who contributes to the inflated load of medical writing with which we are struggling in this age of research and pseudoresearch. Books like this are needed more than ever.

Twenty-one chapters are provided by English, American, Russian, and Dutch workers. Compulsive neurotics and professors who feel that they must stay abreast of everything can relieve their anxiety by keeping this book on their bedside stands, and reading it.

Although the emphasis in this collection is mostly on advanced, scientific aspects of pediatrics, there are three chapters describing the problems of the practicing pediatrician in nonurban areas of Russia, England, and the United States. According to L. M. Sedova, pediatrics in provincial Russia clicks along smoothly. In his district there are about 1,000 children living in two-, three-, and five-story houses provided by the town domiciliary authority. Dr. Sedova averages five or six home visits a day, and holds four sessions of office work a week, lasting about two hours each, plus one prophylactic day. "Due to the wide organization of prophylactic activities and the use of natural factors—sun, air and water—we have very few chronically ill children." "We doctors do not feel isolated in our work. We are always surrounded by colleagues who help us in our difficulties and in the correction of errors." "I improve my medical knowledge by reading the literature, taking part in scientific meetings in our clinic, by attending the scientific pediatric society in Moscow. . . ."

Dr. John Tuthill, describing pediatrics in the United States, finds pediatricians adequate in number and training in nonrural areas only. The country pediatrician is too busy to keep

abreast of the advances in medicine as they are made. There are trends, however, which could correct this, fostered by such programs as those of The Bingham Fund in New England, and the Hunterdon Medical Center in New Jersey.

In England, Dermod MacCarthy finds the general practitioner in command in the average country area. Pediatric consultants, appointed by the National Health Service face serious difficulties, which are, however, being faced and overcome.

The 18 chapters covering recent advances are well written and authoritative. The subjects covered are as follows: Childhood Mortality in England (Logan); Genetics (Carter and Harris); Anoxia in the Newborn (Cross); Neonatal Pathology (Claireaux); Surgery (Zachary); Heart Disease (Reinhold); Hematology (Zeulzer); Viruses (Dudgeon); Malignancy (Steward); Allergy (Frankland); Corticosteroid Therapy (Bongiovanni); Convulsions (Pond); Neurosurgery (Guthkelch); Psychiatry (Winnicott); Metabolism (Stapleton); Chromatography (Jonxis); Radioactive Isotopes (Veall); and Growth (Tanner).

RICHARD L. DAY, M.D.

Epilepsy Handbook. By Frederic A. Gibbs, M.D., and Frederick W. Stamps, M.D. Price, $4.75. Pp. 101, with 8 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

The publication of a handbook by Dr. F. A. Gibbs and Dr. F. W. Stamps is welcome to all who are interested in the problems of clinical epilepsy. Dr. Gibbs and his associates have pioneered the application of electroencephalography for the diagnosis of convulsive disorders in this country, and have originated new concepts which are proving most helpful in the management of children with epilepsy. All who have used the authors' "Atlas of Electroencephalography" will be particularly glad to see the epitome of an unequaled experience in this field, published in such a convenient form.

The preface states that "This book is intended to be a compact, practical compendium of useful knowledge about epilepsy," addressed to "the busy doctor." Initial chapters stress the underlying unity of the epileptic process, whether the seizures are "maximal" or "submaximal," in terms of a disordered and excessive release of energy by the brain, pictured as an electrochemical generator.

This book continues with a brief consideration of various clinical types of convulsive disorder, which improves on such sections in most neurology textbooks in that the various seizure patterns peculiar to young children are stressed. The authors' interest in the ontogeny of epileptic syndromes also assists in making their approach of particular value to the pediatrician.

In general, the functional, reversible, and hopeful nature of convulsive disorders is stressed. The book contains many useful generalizations, such as the observation that inheritable types of epilepsy tend to be relatively benign, and the concept of anticonvulsant medication as a "substitution therapy," that are of value in discussing treatment and outlook with the patient and his family.

The paroxysmal disorders lying on what Gowers described as the "borderland of epilepsy" are well, if briefly, dealt with. This would be expected from the author who described the electrographic 14-and-16-per-second positive spike pattern as a manifestation of an epileptiform disturbance at the diencephalic level, and often accompanied by paroxysmal pain, autonomic or behavioral symptoms of a convulsive equivalent nature.

The discussion of conditions that may be mistaken for seizures which follows is clear and concise, though the statement that "the convulsive seizures that occur after a severe bout of alcoholism are usually not epilepsy" illustrates the type of semantic difficulty which bedevils the definitions in the literature on convulsive disorders. There is a good and up-to-date discussion of the principles of therapy and of the use of individual anticonvulsant drugs, and the book is rounded out by a brief chapter on the handling of a seizure and general counseling. Further excellent features are a compact, tabular summary of epileptic syndromes and their treatment and a colored frontispiece chart for the ready recognition of the more usually used anticonvulsant medications.

Such an authoritative and concise handbook is bound to raise some question as to the degree of emphasis accorded to various subjects. For instance, little is said as to how to arrive at the important decision as to whether an initial seizure is the manifestation of a progressive and potentially dangerous cerebral disease that should be treated in its own right, of a constitutional susceptibility, or, as is most frequent, a sequel to an old cerebral injury, the treatment of which is confined to the control of the convulsive symptoms. To the practicing pediatrician, the question of the amount and nature of the investigation indicated in the

individual case is of great significance, but this is not discussed, whereas other topics, such as the use of antibiotics and corticotropins (ACTH) in hypsarythmia, which reflect the authors' special fields of interest, are stressed. In view of the varying prognosis and etiological uncertainty in this clinically unhomogeneous electrographic entity, such therapeutic measures must be interpreted with great caution.

The authors' emphasis on electroencephalographic techniques provides this book with an individual outlook and the description of the frequent shifts of location and changes in character of electrographically focal lesions with age, illustrates the inadequacy of regarding all such foci as necessarily associated with cerebral pathology in the cortex beneath the appropriate scalp electrode and emphasizes the need for conservatism when considering the advisability of surgical procedures.

In general, this book provides a concise, clearly written, and up-to-date account of their approach to problems of epilepsy by authors of unrivaled experience, and can be heartily recommended.

JOHN S. SCOTT, M.D.

Surgery in Infancy and Childhood. By Matthew White, M.A., M.B., Ch.B., F.R.F.P.S. (Glas.) F.R.C.S. (Edin.), and Wallace M. Dennison, M.D., F.R.F.P.S. (Glas.), F.R.C.S. (Edin.), F.I.C.S. Price, $9.50. Pp. 444, with 267 illustrations. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

This book, as stated in its preface, was designed to introduce to the senior students of Glasgow some of the surgical problems encountered in infancy and childhood and to refresh the memories of the authors' colleagues in general practice. It was not written for the pediatric surgeon as a reference book. It is based mainly on the authors' personal experiences in the Royal Hospital for Sick Children, Glasgow, Scotland, and thus it is in many ways unbalanced in its selection and discussion of surgical problems, with emphasis largely on those disorders seen by the authors with almost no reference to the work of others.

The book covers by brief presentations virtually the entire gamut of pediatric surgical disorders, and, by its survey nature, it necessarily becomes deficient in surgical details. This limitation and its lack of references sharply curtail the usefulness of this volume and make it inadequate as an outline type of synopsis.

One does become impressed with the authors' cognizance of the particular ways children react to illnesses both physically and mentally. They clearly justify the need for pediatric surgery as a specialized branch encompassing all surgical aspects of childhood.

The book is divided by presentation into two parts, five of the first 6 chapters being general in nature and the remaining 19 chapters discussing surgical problems as they pertain to different areas of the body. Two of the more fully discussed sections are in reference to osteomyelitis as seen in the newborn and the problems of trauma to the extremities. Many minor but common problems of childhood are presented quite concisely and clearly; however, as previously noted, many major surgical problems are only superficially discussed.

In summary, one may well enjoy this pleasant, clearly written, easily read book; nevertheless, the incompleteness of details, the lack of references, and the omission of statistics, limit its general usefulness. This book's greatest value undoubtedly would be found when it is supplemented by lectures given by the authors. SAMUEL T. GIAMMONA, M.D.

Recent Advances in Cerebral Palsy. Edited by R. S. Illingworth, M.D. Price, $10. Pp. 389, with 136 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

This book on recent advances in cerebral palsy is edited by R. S. Illingworth, Professor of Child Health, University of Sheffield, England. He has written three of the 15 chapters, including the classification, incidence, and causation of cerebral palsy; early diagnosis and differential diagnosis; and finally the handicaps of the child with cerebral palsy. There are between 1 and 2 cases of cerebral palsy per 1,000 children of school age in Britain as compared with 1½ to 3 in the United States. The classification used is similar to that of the American Academy of Cerebral Palsy, namely, spasticity, athetosis, ataxia, tremor, and rigidity. Two other forms included by the Academy, but omitted by the author, atonic and mixed, are mentioned in the discussion.

In the use of the term cerebral palsy adults are excluded, but heredofamilial degenerative diseases are included. The last is contrary to the recommendation of the American Academy, and poses one of the many difficulties in comparing data of different authors. The editor

stresses that research into the causes of cerebral palsy should be directed toward uncovering the reasons for anoxia, prematurity, antepartum hemorrhage, abortion, and toxemia, as these are the major factors.

In his chapter on structural changes in the brain, Courville refers to congenital malformations, circulatory disturbances and infections in the antenatal period. He concludes that ischemia, anoxia, or both are the chief initiatory causes of many cortical central and ganglionic lesions.

In the chapter on the diagnosis and educational treatment of deafness, Ewing raises the question which has troubled everyone dealing with the cerebral palsied, namely, the educational placement of the child who is palsied and also deaf. Schonell treats of the educational problems and methods of teaching of the cerebral palsied in England. In the main they are similar to those in our own country. Two methods of speech therapy are described. One employs relaxation and a gradual build-up of basic rhythms and patterns of movement; the other makes use of "reflex inhibitory postures" following the Bobath technique of physiotherapy.

There are chapters on the psychological aspects of cerebral palsy; intelligence testing; equipment for the home, school, and treatment clinic; drug therapy; the role of physical therapy and orthopedic surgery in the treatment of cerebral palsy. Myers has an outstanding chapter on recent advances in the neurosurgery of cerberal palsy.

A book of this type, using authors from England, Australia, and the United States offers the reader a variety of ideas. The editor has indicated that he has not attempted to cover the entire field of cerebral palsy, but rather to present an up-to-date review of certain important aspects. In this he has succeeded admirably. One of the major virtues is the inclusion of a comprehensive bibliography by each writer. Attention should also be called to the appendix which presents a summary of the voluntary and tax-supported services for cerebral palsy in the United States.

STANLEY S. LAMM, M.D.

Drugs, Their Nature, Action and Use. By Harry Beckman, M.D. Price, $15. Pp. 728, with 126 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

This book, as is implicit in its title, is an unusual book on pharmacology. It is divided into three sections: The first one is essentially a four-page apology for being a pharmacologist; the second section consists of seven chapters in some 50 pages on general principles in pharmacology, and the last section, entitled "The Actions and Uses of Drugs," constitutes the bulk of the book with 66 chapters in some 600 pages. The organization of the last section is based primarily on clinical usefulness of various drugs, and not on the pharmacodynamic aspects of drug action within the body. Because of this organization many unorthodox, sometimes arbitrary, divisions had to be made in discussing drugs that have diverse biological effects. For instance, the ergot alkaloids are discussed in two parts, one part under "Drugs that Stimulate Uterine Muscle" and another part under "Drugs that Constrict Blood Vessels," the two sections being separated by some 100 pages on drugs that do other things. In a similar manner, the pharacology of the autonomic nervous system is presented with hardly any introductory material on the well-established anatomical and physiological principles of the autonomic nervous system and the viscera that they control. In fact, drug actions on the viscera are discussed separately according to organ systems, and the lack of central pharmacodynamic themes makes it almost impossible to draw any reasonably lucid image of the actions of autonomic mimetic or blocking agents. There are many other examples of arbitrary separation of related material in the book that lead to repetitious pages as well as generalized confusion. The confusion, however, is not limited only to the organization but extends deeply into the choice of material for discussion. On the whole, there is too much superficial encroachment on clinical fields, and not enough discussion of the more fundamental aspects of drug action. The cursory discussions of various clinical problems, while tantalizing to the uninitiated medical student, are not only insufficient, but actually dangerous because they tend to impart shallow misconceptions about complicated clinical situations. The discussions of the pharmacodynamic aspects of drug action are usually out-dated, elementary, and uncritical.

C. Y. KAO

Non-Venereal Syphilis. By Ellis Herndon Hudson, M.D., D.T.M. and H. (Lond.), F.A.C.P., Emeritus Professor and Director of Health, Ohio University. Price, $7. Pp. 197, with 81 illustrations. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

This is a very excellently written book, mostly of the experiences of Dr. Hudson, in studying nonvenereal treponematosis. It is highly recommended for all interested in the treponemal diseases and for those people interested in the effect of ecology on disease. This book is concise, well written and well illustrated.

SIDNEY OLANSKY, M.D.

CORRECTION

On page 53/167 of the February issue of this journal in the article by George B. Logan, M.D., entitled "Mechanisms of the Immediate Allergic Reaction and Some Therapeutic Implications," the first sentence of the first paragraph should read: "One of the early criticisms of the histamine release theory was that this could not explain the decreased coagulability of the blood in anaphylactic shock."

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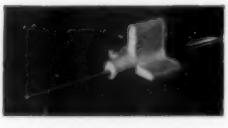

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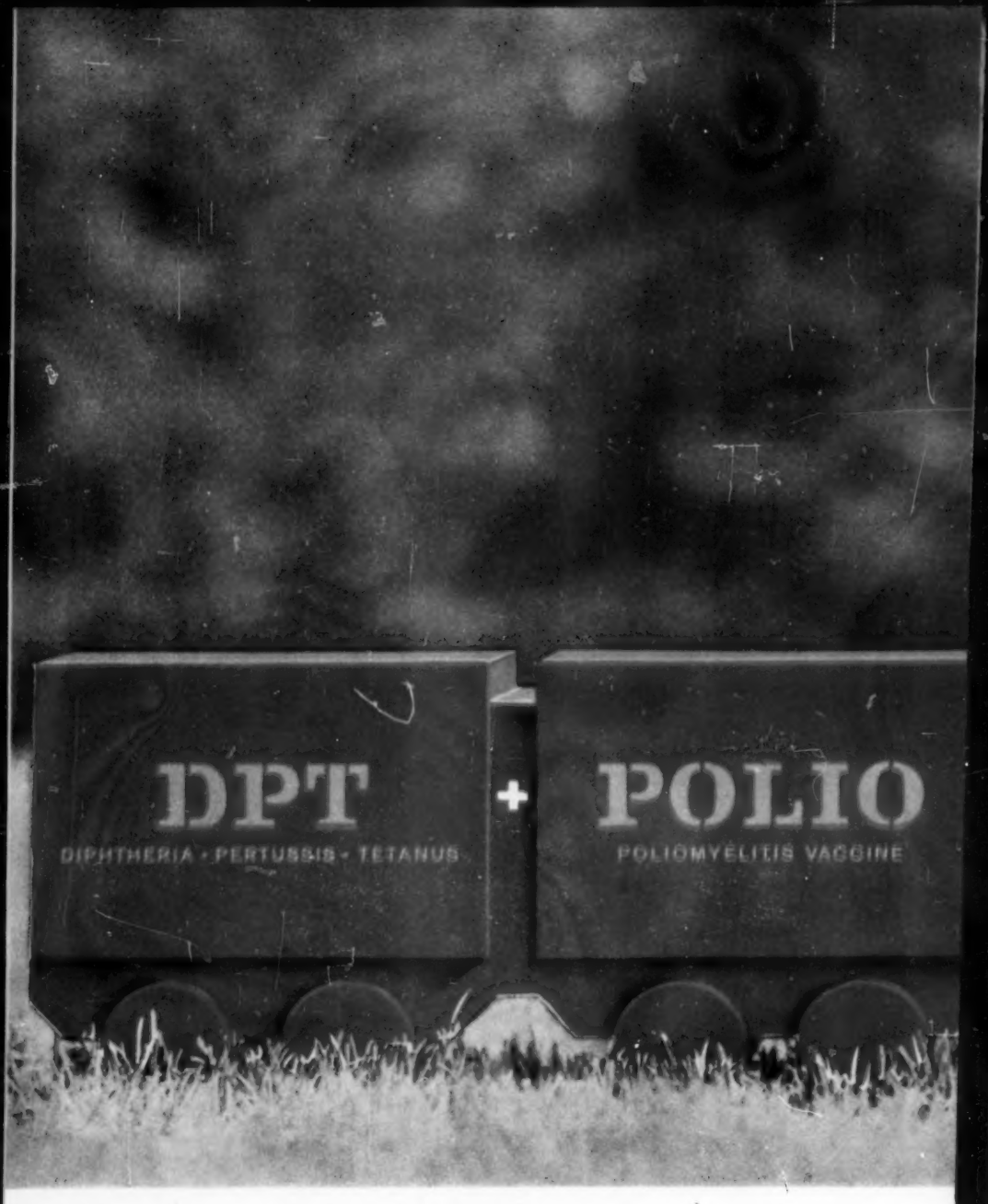

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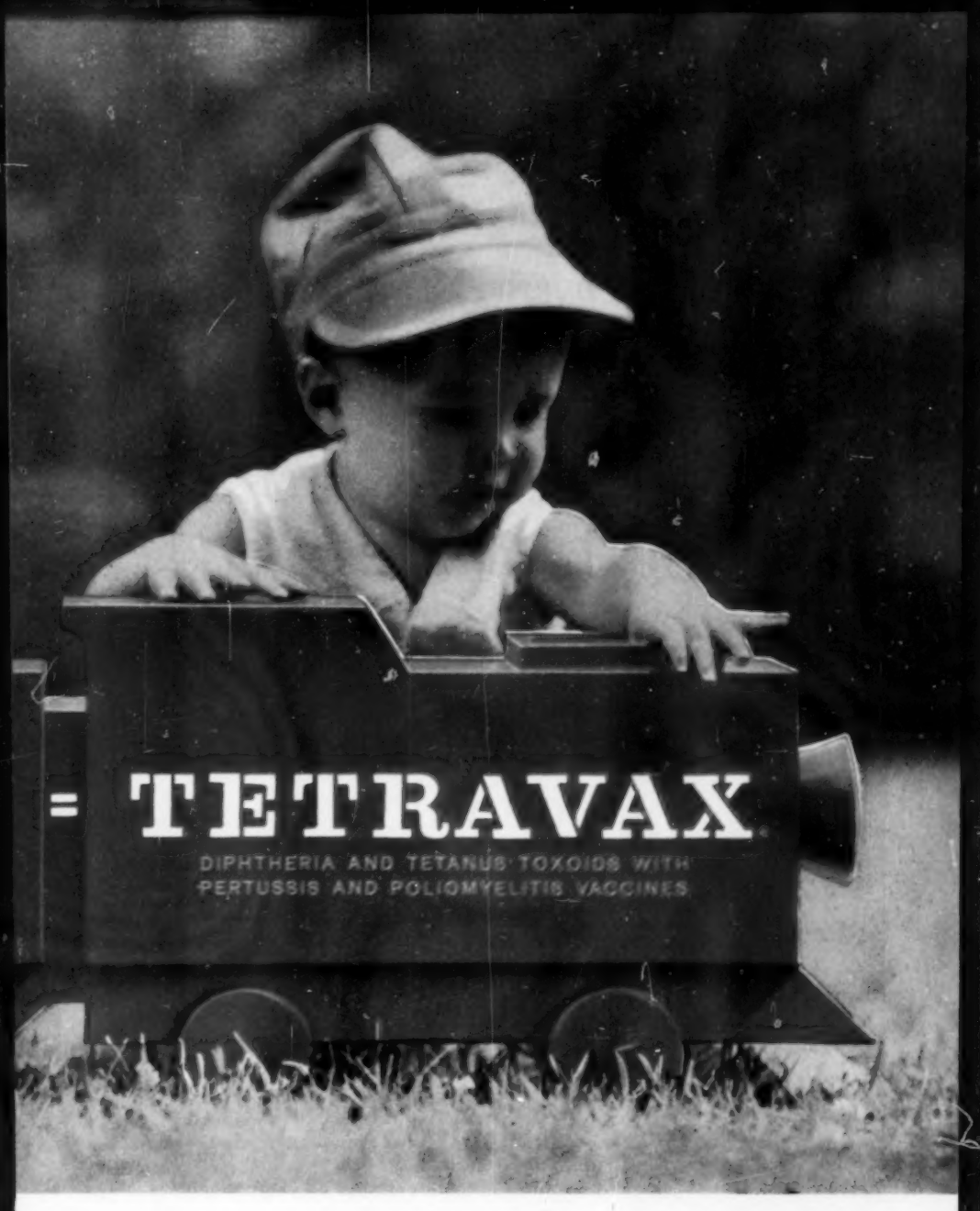

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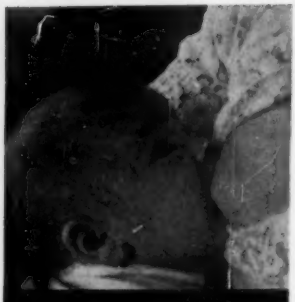

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References: 1. Fomon, S. J., and May, C. D.: Pediatrics *22*:101 (July) 1958. 2. Fomon, S. J.; Thomas, L. N., and May, C. D.: Pediatrics *22*:935 (Nov.) 1958. 3. May, C. D.: Pediatrics *23*:384 (Feb.) 1959. 4. Fomon, S. J., and May, C. D.: Pediatrics *22*:1134 (Dec.) 1958.

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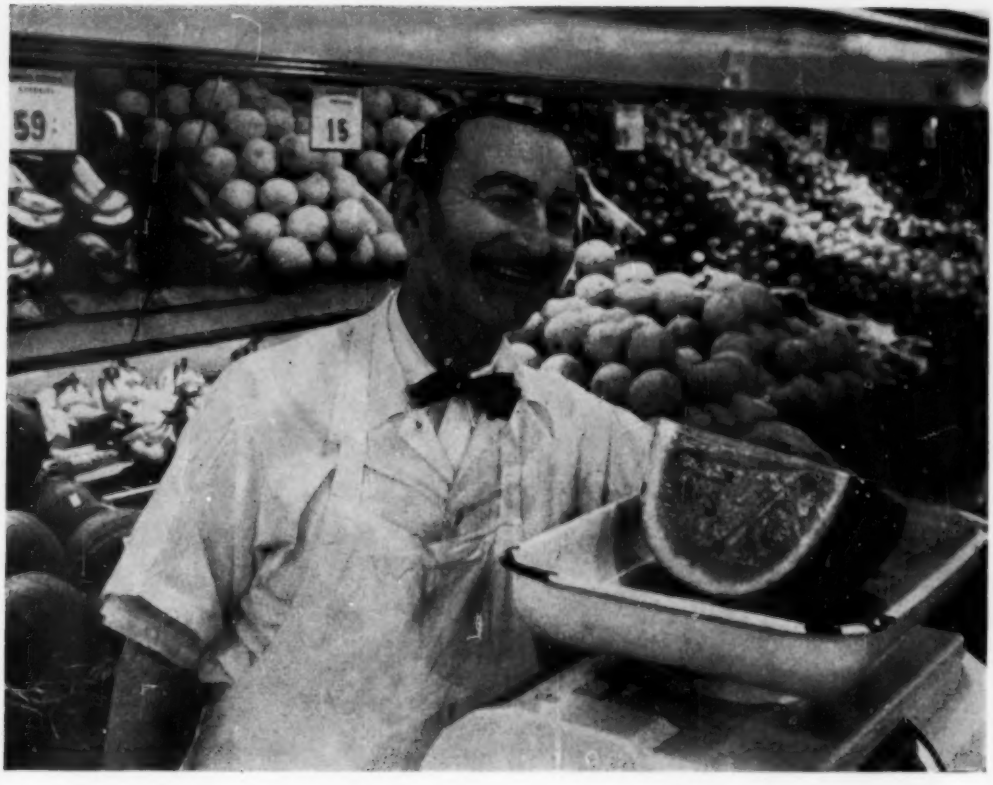

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